UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

In re: SANOFI-AVENTIS SECURITIES LITIGATION	07-CV-10279 (GBD) CLASS ACTION
This document relates to: ALL ACTIONS	**ECF CASE**

NOTICE OF DEFENDANTS' MOTION
TO DISMISS THE AMENDED COMPLAINT

PLEASE TAKE NOTICE that, upon the accompanying Memorandum of Law in Support of Defendants' Motion to Dismiss the Amended Complaint and the Declaration of S. Christopher Provenzano, filed contemporaneously with this Notice of Motion, together with the exhibits identified therein, defendants sanofi-aventis and Douglas Green move this Court, pursuant to the Stipulation Regarding Case Administration, Service and Scheduling Matters, "so-ordered" on February 13, 2008, and Rules 12(b)(6) and 9(b) of the Federal Rules of Civil Procedure, for an order dismissing with prejudice the amended complaint filed in these consolidated actions on April 29, 2008, by lead plaintiffs City of Edinburgh Council of the Lothian Pension Fund and New England Carpenters Guaranteed Annuity Fund and for further relief as the Court deems just and proper.

PLEASE TAKE FURTHER NOTICE that, pursuant to the Stipulation Regarding Case Administration, Service and Scheduling Matters "so-ordered" on February 13, 2008, responses or objections, if any, to this motion shall be in writing, shall state with particularity the reasons for

the objection or response, and shall be filed with the Court and served upon counsel for movants by August 29, 2008.

Dated: New York, New York
June 30, 2008

s/ Lewis J. Liman
Lewis J. Liman, Esq.

CLEARY GOTTLIEB STEEN & HAMILTON LLP
One Liberty Plaza
New York, New York, 10006
T: (212) 225-2000
F: (212) 225-3999

Attorneys for defendant sanofi-aventis and Douglas Greene.

To: Coughlin Stoia Geller Rudman & Robins LLP
Samuel H. Rudman
58 South Service Road, Suite 200
Melville, NY 11747

Coughlin Stoia Geller Rudman & Robins LLP
Tor Gronborg
Trig R. Smith
Laurie L. Largent
655 West Broadway, Suite 1900
San Diego, CA 92101-3301

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

In re: SANOFI-AVENTIS SECURITIES LITIGATION	07-CV-10279 (GBD) CLASS ACTION
This document relates to: ALL ACTIONS	**ECF CASE**

DECLARATION OF S. CHRISTOPHER PROVENZANO IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS THE AMENDED COMPLAINT

I, S. CHRISTOPHER PROVENZANO, declare as follows:

1. I am associated with the law firm of Cleary Gottlieb Steen & Hamilton LLP, attorneys for sanofi-aventis ("sanofi") and Douglas Greene (together, the "Defendants") in this action. I am also a member of the bar of this Court.

2. I submit this Declaration in support of Defendants' memorandum of law in support of their motion to dismiss, pursuant to Rules 12(b)(6) and 9(b) of the Federal Rules of Civil Procedure, the amended complaint filed in these consolidated actions (the "Amended Complaint") on April 29, 2008, by lead plaintiffs City of Edinburgh Council of the Lothian Pension Fund and New England Carpenters Guaranteed Annuity Fund (together, "Plaintiffs"). The purpose of this declaration is to put before the Court documents incorporated by reference in the Amended Complaint.

3. Attached hereto as Exhibit A is a true and complete copy of the RIO-Europe study, as published in The Lancet on April 16, 2005, incorporated by reference in the Amended Complaint at paragraphs 23, 31, 66-68, 70, 79, and 87.

4. Attached hereto as Exhibit B is a true and complete copy of the RIO-Lipids study, as published in The New England Journal of Medicine on November 17, 2005, incorporated by reference in the Amended Complaint at paragraphs 23 and 87.

5. Attached hereto as Exhibit C is a true and complete copy of the RIO-North America study, as published in the Journal of the American Medical Association on February 15, 2006, incorporated by reference in the Amended Complaint at paragraphs 23, 52, 70, 80, and 87.

6. Attached hereto as Exhibit D is a true and complete copy of the RIO-Diabetes study, as published in The Lancet on November 11, 2006, incorporated by reference in the Amended Complaint at paragraphs 23, 74, 79, 87, 102, and 109.

7. Attached hereto as Exhibit E is a true copy of relevant excerpts of sanofi's Form 20-F for the year 2004, incorporated by reference in the Amended Complaint at paragraph 70.

8. Attached hereto as Exhibit F is a true and complete copy of a transcript of sanofi's conference call dated March 1, 2005, discussing Q4 2004 earnings, incorporated by reference in the Amended Complaint at paragraph 66.

9. Attached hereto as Exhibit G is a true and complete copy of a transcript of sanofi's conference call dated March 9, 2005, discussing the results of the RIO-Europe study, incorporated by reference in the Amended Complaint at paragraphs 27-28, 55, and 68-69.

10. Attached hereto as Exhibit H is a true and complete copy of a transcript of sanofi's conference call dated June 13, 2005, discussing the results of the RIO-Diabetes study, incorporated by reference in the Amended Complaint at paragraph 74.

11. Attached hereto as Exhibit I is a true and complete copy of sanofi's press release dated June 23, 2005, incorporated by reference in the Amended Complaint at paragraph 75.

12. Attached hereto as Exhibit J is a true and complete copy of a transcript of sanofi's conference call dated August 31, 2005, discussing Q2 2005 earnings, incorporated by reference in the Amended Complaint at paragraph 78.

13. Attached hereto as Exhibit K is a true copy of relevant excerpts of sanofi's Form 20-F for the year 2005, incorporated by reference in the Amended Complaint at paragraph 93.

14. Attached hereto as Exhibit L is a true and complete copy of sanofi's press release dated February 14, 2006, incorporated by reference in the Amended Complaint at paragraph 80.

15. Attached hereto as Exhibit M is a true and complete copy of sanofi's press release dated February 17, 2006, incorporated by reference in the Amended Complaint at paragraphs 61, 63, and 83.

16. Attached hereto as Exhibit N is a true and complete copy of a transcript of sanofi's conference call dated February 24, 2006, discussing Q4 2005 earnings, incorporated by reference in the Amended Complaint at paragraphs 15 and 86-89.

17. Attached hereto as Exhibit O is a true and complete copy of a transcript of sanofi's New York Analyst Meeting and Conference Call on March 22, 2006, incorporated by reference in the Amended Complaint at paragraphs 33, 55 and 90-92.

18. Attached hereto as Exhibit P is a true and complete copy of sanofi's press release dated April 28, 2006, incorporated by reference in the Amended Complaint at paragraph 95.

19. Attached hereto as Exhibit Q is a true and complete copy of a transcript of sanofi's conference call dated May 5, 2006, discussing Q1 2006 earnings, incorporated by reference in the Amended Complaint at paragraphs 17 and 96.

20. Attached hereto as Exhibit R is a true and complete copy of sanofi's press release dated June 21, 2006, incorporated by reference in the Amended Complaint at paragraph 99.

21. Attached hereto as Exhibit S is a true and complete copy of a transcript of sanofi's conference call dated August 2, 2006, discussing Q2 2006 earnings, incorporated by reference in the Amended Complaint at paragraph 100.

22. Attached hereto as Exhibit T is a true and complete copy of sanofi's press release dated October 27, 2006, incorporated by reference in the Amended Complaint at paragraph 102.

23. Attached hereto as Exhibit U is a true and complete copy of a transcript of sanofi's conference call dated October 31, 2006, discussing Q3 2006 earnings, incorporated by reference in the Amended Complaint at paragraph 103.

24. Attached hereto as Exhibit V is a true and complete copy of sanofi's press release dated October 31, 2006, incorporated by reference in the Amended Complaint at paragraph 104.

25. Attached hereto as Exhibit W is a true and complete copy of sanofi's slide presentation labeled Crédit-Suisse Conference, dated November 9, 2006, incorporated by reference in the Amended Complaint at paragraph 106 available at http://en.sanofi-aventis.com/Images/061109_acomplia_cs_en_tcm24-14692.pdf.

26. Attached hereto as Exhibit X is a true and complete copy of a transcript of sanofi's conference call dated December 5, 2006, discussing the results of the SERENADE study, incorporated by reference in the Amended Complaint at paragraphs 109-10.

27. Attached hereto as Exhibit Y is a true and complete copy of sanofi's press release dated December 5, 2006, incorporated by reference in the Amended Complaint at paragraph 111.

28. Attached hereto as Exhibit Z is a true and complete copy of sanofi's press release dated December 8, 2006, incorporated by reference in the Amended Complaint at paragraph 112.

29. Attached hereto as Exhibit AA is a true copy of relevant excerpts of sanofi's Form 20-F for the year 2006, incorporated by reference in the Amended Complaint at paragraph 119.

30. Attached hereto as Exhibit BB is a true and complete copy of sanofi's conference call dated February 13, 2007, discussing Q4-2006 earnings, incorporated by reference in the Amended Complaint at paragraph 114.

31. Attached hereto as Exhibit CC is a true and complete copy of sanofi's press release dated February 13, 2007, incorporated by reference in the Amended Complaint at paragraph 115.

32. Attached hereto as Exhibit DD is a true and complete copy of sanofi's press release dated March 26, 2007, incorporated by reference in the Amended Complaint at paragraph 118.

33. Attached hereto as Exhibit EE is a true and complete copy of a transcript of sanofi's conference call dated May 3, 2007, discussing Q1 2007 earnings, incorporated by reference in the Amended Complaint at paragraph 121.

34. Attached hereto as Exhibit FF is a true and complete copy of sanofi's press release dated May 3, 2007, incorporated by reference in the Amended Complaint at paragraph 122.

35. Attached hereto as Exhibit GG is a true and complete copy of sanofi's press release dated June 13, 2007, incorporated by reference in the Amended Complaint at paragraphs 36 and 125.

36. Attached hereto as Exhibit HH is a true and complete copy of the transcript of the June 13, 2007, meeting of the United States Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee Meeting (the "Advisory Committee"), incorporated by reference in the Amended Complaint at paragraphs 25, 28, 34-39, 61, 63-64, 118, 121-22, 125-32, and 139, available at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic. True and complete

copies of the slide presentations given by presenters during their testimony before the Advisory Committee and referenced in that testimony are included below as separate exhibits.

37. Attached hereto as Exhibit II is a true and complete copy of the slide presentation given by Kelly Posner, Ph.D., as part of her testimony to the Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-01-CU-Posner.ppt.

38. Attached hereto as Exhibit JJ is a true and complete copy of the slide presentation given by Richard Gural, Ph.D., as part of his testimony to the Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-02-Sanofi-Aventis-Gural.pdf.

39. Attached hereto as Exhibit KK is a true and complete copy of the slide presentation given by Paul Chew, M.D., as part of his testimony to the Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-05-Sanofi-Aventis-Chew.pdf.

40. Attached hereto as Exhibit LL is a true and complete copy of the slide presentation given by Amy Egan, M.D., as part of her testimony to the Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-10-FDA-Egan.ppt.

Pursuant to 28 U.S.C. § 1746(a), I declare under penalty of perjury that the foregoing is true and correct. Executed on June 27, 2008.

s/ S. Christopher Provenzano
S. Christopher Provenzano

Exhibit A

NYPL RESEARCH LIBRARIES
3 3433 06309042 1
Case 1:07-cv-10279-GBD Document 23-3 Filed 06/30/2008 Page 2 of 12
DELIVERY DESK SIBL
The Lancet.
v. 365
no. 9468
Apr 16-22, 2005
Vol. 363:9428-9431, 9435
claimed with READ 9/23/04

ELSEVIER

THE LANCET

Volume 365 Number 9468 Pages 1361–438 April 16–22, 2005

www.thelancet.com

"... a smallpox pandemic is likely; ordinary methods of public health cannot control person-to-person infections; and vaccine stores are the key to control. Poppycock, poppycock, poppycock!"

See **Comment** page 1370

LAU/0516/03356778-5/S/LAD 01 00/002
SCIENC, IND. & BUSIN/LANCET416 0142
NEW YORK PUBLIC LIBRARY
BRAND CENTRAL STATION
PO BOX 2233 NY 10163 2233

Editorial
Anaesthesia during lethal injection
See page 1361

Correspondence
Pope John Paul II
See page 1383

Articles
RIO-Europe study
See page 1389

Mechanisms of Disease
Paraneoplastic stiff-person syndrome
See page 1406

Seminar
The metabolic syndrome
See page 1415

THE LANCET

Volume 365 Number 9468 April 16–22, 2005

Editorial

1361 Medical collusion in the death penalty: an American atrocity

1362 China must not neglect reform of primary care

1362 Jeffrey Sachs' "punk-rock" appeal to the Nobel committee

Comment

1363 Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors
U Pagotto, R Pasquali

1365 A step forward for stiff-person syndrome
T M Burns

1367 Screening for pre-eclampsia: the quest for the Holy Grail?
F Audibert

1369 Bruising in children
E Cabinum-Foeller, L Frasier

1370 The ghost of pandemics past
T M Mack

1372 Should physicians' self-prescribing be restricted by law?
E O Rosvold, R Tyssen

World Report

1375 Doctor sues clinic over Yushchenko poisoning claims
E Holt

1376 The battle for child rights in Pakistan
K Ahmad

1378 India's new patent laws may still hurt generic drug supplies
P Chatterjee

Perspectives

1379 Book: An end to poverty or more of the same?
P Townsend

1380 In brief
C Cooper; K Morris

1381 Historical keywords
C Lawrence

1381 Lifeline
A McNab

Obituary

1382 Sir John Vivian Dacie
P Wright

Correspondence

1383 The Pope's grievous errors
P Mane; A Szczeklik

1383 Treatment of hepatic encephalopathy
A T Blei; J Córdoba and others; J M Walshe; R Jalan, D Shawcross

1386 Preventing obesity: a public health priority in Spain
M Neira, M de Onis

1386 Alcohol and public health
M J Miguez-Burbano, J Jackson Jr; A Braillon, G Dubois

1387 Influence of violent media on children and adolescents
M Spitzer

1388 Could these be gallstones?
C W Sies, J Brooker

Articles

1389 Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients
L F Van Gaal

1398 Prevalence of the metabolic syndrome and overweight among adults in China
D Gu and others

Mechanisms of Disease

1406 Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin (WebExtra)
C Sommer and others

Research Letters

1412 Inadequate anaesthesia in lethal injection for execution (Peer reviewed and fast-tracked)
L G Koniaris and others

Seminar

1415 The metabolic syndrome
R H Eckel and others

Series

1429 Epidemiology 2
Compared to what? Finding controls for case-control studies
D A Grimes, K F Schulz

Essay

1434 Time and chance: the stochastic nature of disease causation
D I W Coggon, C N Martyn

Case Report

1438 A child with painful legs
P Rosati and others

➔ Peer reviewed and fast-tracked to publication in 4 weeks

WebExtra content

International Advisory Board

Karen Antman (Bethesda)
Valerie Beral (Oxford)
Robert Beaglehole (Geneva)
Robert Fletcher (Boston)
Suzanne Fletcher (Boston)
Karen Gelmon (Vancouver)
Johan Giesecke (Stockholm)
David Grimes (Durham)
Keiichi Hiramatsu (Tokyo)
Jay Levy (San Francisco)
Sue Lightman (London)
Judith Lumley (Melbourne)
Elizabeth Molyneux (Blantyre)
Alwyn Mwinga (Lusaka)
Marie-Louise Newell (London)
Stuart Pocock (London)
Giuseppe Remuzzi (Bergamo)
Ken Schulz (Chapel Hill)
Frank Shann (Melbourne)
Anne Tattersfield (Nottingham)
Chris Van Weel (Nijmegen)
Jan Vandenbroucke (Leiden)
David Weatherall (Oxford)
Nick White (Bangkok)

The Lancet—London
32 Jamestown Road
London NW1 7BY
North American Editor
Michael McCarthy
T +1 206 706 7461
Contributing Editors
Dorothy Bonn
Dan Greenberg
William Jeffcoate
Marilyn Larkin
Fiona Matthews
Rosalind Osmond
David Sharp
Information for Authors
www.thelancet.com

Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study

*Luc F Van Gaal, Aila M Rissanen, André J Scheen, Olivier Ziegler, Stephan Rössner, for the RIO-Europe Study Group**

Lancet 2005; 365: 1389–97

*Members listed at end of paper

Department of Diabetology, Metabolism, and Clinical Nutrition, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem-Antwerp, Belgium (L F Van Gaal); **Obesity Research Unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland** (A M Rissanen); **Division of Diabetes, Nutrition, and Metabolic Disorders, University of Liege, Liege, Belgium** (A J Scheen); **Service de Diabétologie, Maladies Métaboliques, Maladies de la Nutrition Hôpital Jeanne d'Arc, CHU de Nancy, Toul, France** (O Ziegler); **and Obesity Unit, Huddinge University Hospital, Huddinge, Sweden** (S Rössner)

Correspondence to: Prof Luc Van Gaal **luc.van.gaal@uza.be**

Summary

Background **In animal models, cannabinoid-1 receptor (CB_1) blockade produces a lean phenotype, with resistance to diet-induced obesity and associated dyslipidaemia. We assessed the effect of rimonabant, a selective CB_1 blocker, on bodyweight and cardiovascular risk factors in overweight or obese patients.**

Methods **1507 patients with body-mass index 30 kg/m² or greater, or body-mass index greater than 27 kg/m² with treated or untreated dyslipidaemia, hypertension, or both, were randomised to receive double-blind treatment with placebo, 5 mg rimonabant, or 20 mg rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit). The primary efficacy endpoint was weight change from baseline after 1 year of treatment in the intention-to-treat population.**

Findings **Weight loss at 1 year was significantly greater in patients treated with rimonabant 5 mg (mean –3·4 kg [SD 5·7]; p=0·002 *vs* placebo) and 20 mg (–6·6 kg [7·2]; p<0·001 vs placebo) compared with placebo (–1·8 kg [6·4]). Significantly more patients treated with rimonabant 20 mg than placebo achieved weight loss of 5% or greater (p<0·001) and 10% or greater (p<0·001). Rimonabant 20 mg produced significantly greater improvements than placebo in waist circumference, HDL-cholesterol, triglycerides, and insulin resistance, and prevalence of the metabolic syndrome. The effects of rimonabant 5 mg were of less clinical significance. Rimonabant was generally well tolerated with mild and transient side effects.**

Interpretation **CB_1 blockade with rimonabant 20 mg, combined with a hypocaloric diet over 1 year, promoted significant decrease of bodyweight and waist circumference, and improvement in cardiovascular risk factors.**

Introduction

The prevalence of obesity continues to increase, with more than 50% of Europeans currently classified as overweight and up to 30% as clinically obese.[1,2] WHO has estimated that, yearly, about a quarter of a million deaths in Europe and more than 2·5 million deaths worldwide are weight-related, with cardiovascular disease as the leading cause.[3] Because few safe and effective drugs are available, the treatment of obesity remains one of the greatest unmet clinical needs of our time.

The newly discovered endocannabinoid system contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects.[4–6] This system consists of endogenous ligands and two types of G-protein-coupled cannabinoid receptors: CB_1, located in several brain areas and in a variety of peripheral tissues including adipose tissue, the gastrointestinal tract, the pituitary and adrenal glands, sympathetic ganglia, heart, lung, liver, and urinary bladder;[7,8] and CB_2, in the immune system.[9] The endocannabinoid system is overactivated in genetic animal models of obesity[5] and in response to exogenous stimuli such as excessive food intake.[10] Preclinical studies implicate the endocannabinoid system in the modulation of food intake and adipogenesis,[11–13] through peripheral mechanisms. The system might provide a possible treatment target for high-risk overweight or obese patients. Insights into the endocannabinoid system have been derived from studies in animals with genetic deletion of CB_1, which have a lean phenotype and are resistant to diet-induced obesity and associated insulin resistance produced by a highly palatable high-fat diet.[14] Further evidence comes from investigation of pharmacological blockade of CB_1 receptors with the selective CB_1 blocker rimonabant, which produces weight loss and ameliorates metabolic abnormalities in obese animals.[10,15] Preclinical findings support the role of the CB_1 receptor in both central and peripheral regulation of energy balance and body weight,[5] providing a mechanistic basis for the clinical development of rimonabant for the management of obesity and associated cardiovascular risk factors.

We undertook a large, multicentre, multi-national, randomised, placebo-controlled trial—the RIO (Rimonabant In Obesity) Europe trial—to assess the efficacy and safety of rimonabant in reducing body weight and improving cardiovascular risk factors in overweight or obese patients.

Methods

Patients

Men and women aged 18 years or older, with body-mass index (BMI) 30 kg/m² or greater, or BMI greater than 27 kg/m² with treated or untreated hypertension or

treated or untreated dyslipidaemia, were recruited from 60 sites in Europe and the USA between October, 2001, and April, 2002. Although RIO-Europe was planned to be done in Europe only, difficulties in meeting recruitment targets led to the extension of the study to 20 sites in the USA with an enrolment, of 276 US patients.

Eligible patients had less than 5 kg variation in bodyweight within the 3 months before study entry. Exclusion criteria included clinical disorders, such as substantial endocrine disease, diabetes mellitus, cardiovascular or pulmonary disease, hepatic and renal disorders, or substantial neurological or psychological illness. Patients were also excluded if they had a history of depression necessitating hospitalisation, two or more recurrent episodes of depression, or suicide attempt. Previous history of surgical procedures for weight loss (eg, stomach stapling, bypass) was also an exclusion criterion. Concomitant use of medications known to alter bodyweight or appetite, including anti-obesity drugs, corticosteroids, antidepressants, neuroleptics, non-selective systemic antihistamines, nicotine substitutes, and antidiabetic drugs, was not permitted. No change in hypolipidaemic medication was allowed. To avoid metabolic effects due to altered smoking habits, patients who indicated their intention to stop smoking were not included. Marijuana and hashish users were excluded from the study.

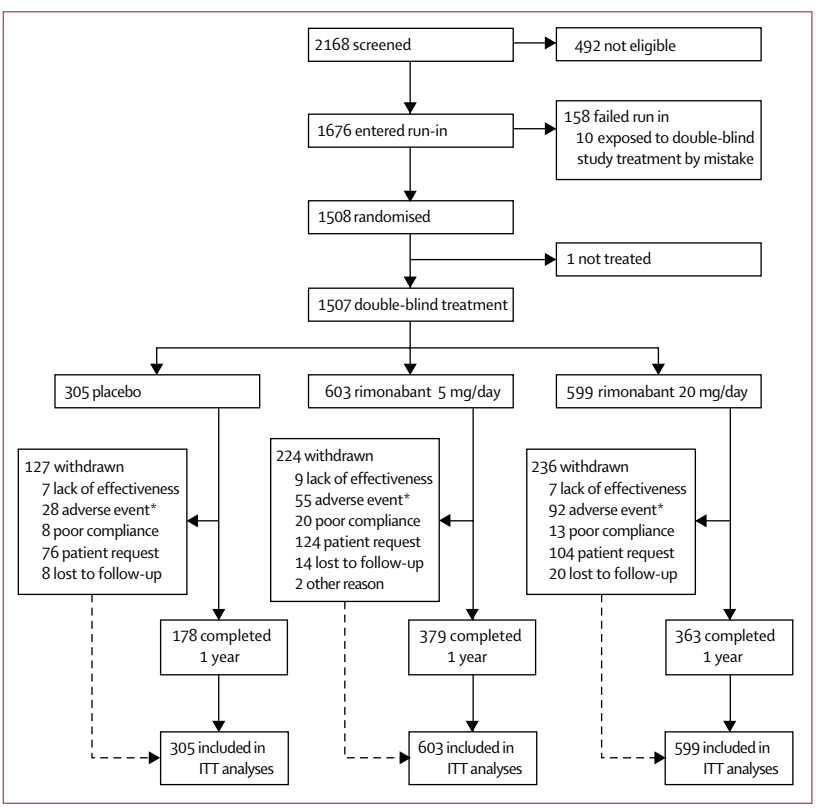


Figure 1: **Trial profile**
*Including run-in period.

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Race (white)*	290 (95·1%)	565 (93·7%)	555 (92·7%)
Sex (female) *	244 (80·0%)	476 (78·9%)	478 (79·8%)
Age (years)†	45·0 (11·6)	45·4 (11·2)	44·6 (11·9)
BMI (kg/m²)†	35·7 (5·9)	36·0 (5·9)	36·2 (5·8)
Weight (kg) †	100·0 (20·3)	100·9 (19·8)	101·7 (19·5)
Waist (cm)†	107·7 (13·8)	108·4 (14·3)	108·8 (14·1)
Hypertension (%)*	116 (38·0%)	264 (43·8%)	237 (39·6%)
Dyslipidaemia (%)*	189 (62·0%)	371 (61·5%)	355 (59·4%)
Metabolic syndrome (%)*	121 (40·6%)	243 (40·8%)	251 (42·4%)
Current smokers (%)*	60 (19·7%)	136 (22·6%)	102 (17·0%)

*Data are number (%). †Data are mean (SD).

Table 1: **Baseline characteristics**

Procedures

The study was approved by the local ethics committees and done in accordance with the Declaration of Helsinki and ICH Good Clinical Practice between October, 2001, and June, 2004. RIO-Europe was a 2-year randomised, double-blind, placebo-controlled, parallel group, fixed-dose, multicentre study, with a 2-week screening period and 4-week single-blind, placebo run-in period. For the double-blind treatment period, the randomisation code list, with a block size of five, was generated centrally by the sponsor. Treatments were allocated to patients using the interactive voice responding system according to the predefined randomisation list (1: 2: 2 ratio for placebo, 5 mg rimonabant, and 20 mg rimonabant, respectively). A central laboratory (ICON Laboratories, Farmingdale, USA, and Dublin, Ireland) ensured that the randomisation of treatment was balanced within each centre and was stratified based on the loss of bodyweight (⩽2 kg or >2 kg) recorded during the run-in period, per protocol. During the double-blind period, patients were seen every 14 days during the first month and thereafter every 28 days until the end of the study.

Basal metabolic rate was estimated with the Harris Benedict formula, and 600 kcal were subtracted by a dietician to calculate a recommended daily energy intake for each patient. At each visit, patients received dietary counselling and were encouraged to increase physical activity.

Bodyweight, waist circumference, and blood pressure were measured at screening, at randomisation, and at every treatment visit, whereas lipid profile, fasting glucose, and insulin were measured every 3 months by use of standard procedures in the central laboratory (ICON Laboratories).[16] Hypertension was defined as systolic/diastolic blood pressure of 140/90 mm Hg or greater. Dyslipidaemia was defined as LDL-cholesterol 3·36 mmol/L or greater, HDL-cholesterol less than 1·03 mmol/L, and triglycerides 1·69 mmol/L or greater. The prevalence of the metabolic syndrome was assessed at screening, baseline, and 12 months, according to the criteria of the National Cholesterol Education Program

Adult Treatment Panel III.[17] An oral glucose tolerance test (75 g glucose) was done at baseline and at 1 year.

The primary efficacy endpoint was the absolute weight change from baseline (randomisation) at the end of year 1 in the intention-to-treat (ITT) population. Another weight-related criterion was the proportion of patients who achieved weight loss of 5% or more and 10% or more. Secondary efficacy endpoints were waist circumference (as a marker of change in abdominal obesity), concentrations of glucose and insulin in serum when fasting, HDL-cholesterol and triglycerides, and the prevalence of the metabolic syndrome. Additional efficacy endpoints were changes in concentrations of total cholesterol and LDL-cholesterol in serum and changes in insulin resistance, derived from the HOMA-IR (homoeostasis model assessment), calculated as fasting insulin (μU/mL)×fasting glucose (mmol/L)/22·5.[18] Analysis of quality of life and dietary assessment were also done at baseline and after 1 year (data still under analysis).

Safety assessments, including physical examination, standard laboratory tests (haematology, liver enzymes, blood chemistry tests), and an ECG, were done at screening, at baseline, and at regular visits every 3 months. Adverse events were recorded at each visit. Mood was evaluated with the Hospital Anxiety and Depression (HAD) scale[19] at baseline and every 3 months. Patients who presented with a symptom of depression or an HAD score of 11 or greater had to be referred to a psychiatrist to ascertain the exact diagnosis of the clinical picture, and treatment if indicated. The HAD score is a short, self-report scale, which is easy to use in a primary-care setting to screen for the presence of mood disorders in different populations of patients, including obese patients.[19] An independent Data Safety Monitoring Board was in place to ensure the safety of the patients by review and analysis of the unblinded safety data, on a regular basis.

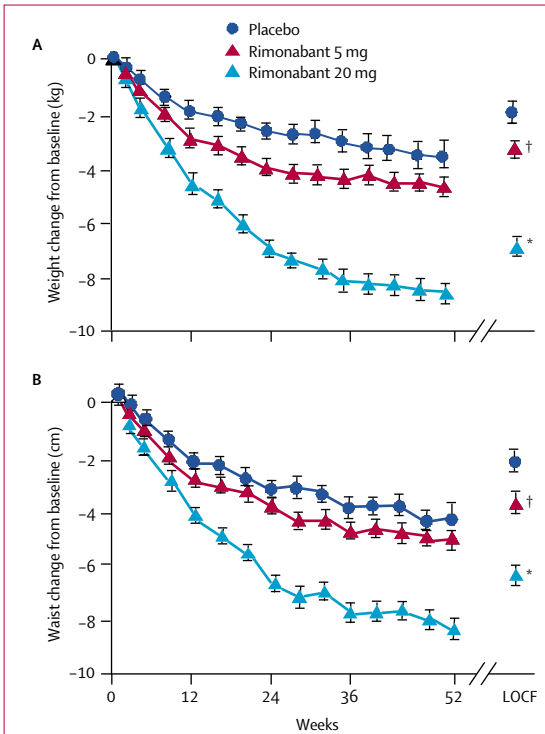


Figure 2: **Change from baseline in bodyweight (A) and waist circumference (B)**
Data are mean (SE) values for patients completing each scheduled visit, and LOCF (values for the full ITT population with the last observations carried forward). *p<0·001 *vs* placebo. †p=0·002 *vs* placebo.

	Placebo	Rimonabant		p *vs* placebo	
		5 mg	20 mg	5 mg	20 mg
Weight (kg)					
Baseline	99·9 (20·2)	100·7 (19·7)	101·7 (19·4)		
1 year	98·1 (20·9)	97·3 (20·1)	95·1 (20·6)		
Change	−1·8 (6·4)	−3·4 (5·7)	− 6·6 (7·2)	0·002	<0·001
Waist (cm)					
Baseline	107·7 (13·8)	108·3 (14·3)	108·7 (14·1)		
1 year	105·3 (14·3)	104·4 (14·5)	102·2 (15·4)		
Change	−2·4 (6·9)	−3·9 (6·3)	−6·5 (7·4)	0·002	<0·001
SBP (mm Hg)					
Baseline	126·8 (13·7)	127·0 (14·8)	127·0 (14·1)		
1 year	127·0 (13·6)	126·1 (14·7)	126·0 (14·1)		
Change	0·3 (12·3)	−0·9 (12·5)	−1·0 (12·5)	ns	ns
DBP (mm Hg)					
Baseline	79·7 (8·5)	79·6 (9·1)	79·4 (8·8)		
1 year	79·8 (8·7)	78·8 (8·9)	78·5 (8·6)		
Change	0·1 (8·5)	− 0·8 (8·8)	− 0·9 (8·7)	ns	ns
TC (mmol/L)					
Baseline	5·29 (1·00)	5·37 (0·92)	5·37 (1·00)		
1 year	5·37 (1·01)	5·43 (0·86)	5·42 (0·98)		
Change	0·08 (0·78)	0·06 (0·70)	0·05 (0·70)	ns	ns
HDL-C (mmol/L)					
Baseline	1·27 (0·34)	1·27 (0·32)	1·27 (0·33)		
1 year	1·42 (0·38)	1·46 (0·37)	1·54 (0·40)		
Change	0·15 (0·23)	0·19 (0·23)	0·26 (0·26)	0·048	<0·001
TG (mmol/L)					
Baseline	1·45 (0·87)	1·46 (0·89)	1·45 (0·85)		
1 year	1·43 (0·78)	1·44 (0·92)	1·25 (0·72)		
Change	−0·01 (0·68)	−0·02 (0·77)	−0·20 (0·64)	ns	<0·001
LDL-C (mmol/L)					
Baseline	3·13 (0·82)	3·19 (0·76)	3·21 (0·81)		
1 year	3·30 (0·88)	3·32 (0·75)	3·29 (0·83)		
Change	0·17 (0·70)	0·13 (0·62)	0·08 (0·63)	ns	ns
Total/HDL-C ratio					
Baseline	4·42 (1·28)	4·46 (1·22)	4·44 (1·21)		
1 year	3·99 (1·15)	3·94 (1·11)	3·72 (1·06)		
Change	−0·42 (0·83)	−0·52 (0·80)	−0·71 (0·78)	ns	<0·001
Fasting glucose (mmol/L)					
Baseline	5·26 (0·70)	5·30 (0·62)	5·28 (0·70)		
1 year	5·29 (0·83)	5·26 (0·73)	5·20 (0·68)		
Change	0·03 (0·77)	−0·05 (0·68)	−0·09 (0·65)	ns	0·026
Fasting insulin (mU/mL)					
Baseline	12·4 (9·6)	12·7 (9·2)	12·7 (9·5)		
1 year	14·2 (13·1)	13·0 (10·5)	11·7 (8·3)		
Change	1·8 (13·0)	0·3 (11·2)	−1·0 (8·8)	ns	<0·001
HOMA–IR (%)					
Baseline	3·0 (2·6)	3·1 (2·8)	3·1 (2·5)		
1 year	3·4 (3·5)	3·1 (2·9)	2·8 (2·3)		
Change	0·4 (3·5)	0·0 (3·4)	−0·3 (2·4)	ns	0·002

Data are mean (SD). Analyses for total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were done on percentage changes from baseline, and those for cholesterol ratios were done on changes from baseline. SBP=systolic blood pressure. DBP=diastolic blood pressure. ns=not significant.

Table 2: **Changes in metabolic and cardiovascular risk factors in ITT population**

	Placebo	Rimonabant		p *vs* placebo	
		5 mg	20 mg	5 mg	20 mg
Weight (kg)					
Baseline	98·5 (19·7)	100·1 (19·6)	102·0 (19·7)		
1 year	94·9 (20·0)	95·4 (19·8)	93·4 (20·8)		
Change	−3·6 (7·4)	−4·8 (6·2)	−8·6 (7·3)	0·042	<0·001
Waist (cm)					
Baseline	108·0 (13·8)	109·0 (14·2)	109·3 (14·4)		
1 year	103·5 (14·3)	103·7 (14·7)	100·8 (15·5)		
Change	−1·5 (7·3)	−5·3 (6·4)	−8·5 (7·4)	ns	<0·001
SBP (mmHg)					
Baseline	127·1 (13·8)	127·4 (14·7)	127·8 (14·1)		
1 year	126·7 (13·7)	126·1 (15·1)	125·8 (13·5)		
Change	−0·4 (12·7)	−1·3 (12·2)	−2·0 (12·6)	ns	ns
DBP (mmHg)					
Baseline	80·2 (8·0)	79·6 (9·3)	79·7 (9·0)		
1 year	79·8 (8·2)	78·2 (9·0)	78·0 (8·5)		
Change	−0·4 (8·1)	−1·5 (8·8)	−1·8 (8·7)	ns	ns
LDL-C (mmol/L)					
Baseline	3·12 (0·81)	3·22 (0·77)	3·18 (0·79)		
1 year	3·33 (0·87)	3·36 (0·75)	3·28 (0·82)		
Change	0·21 (0·70)	0·13 (0·61)	0·10 (0·63	ns	0·024
HDL-C (mmol/L)					
Baseline	1·28 (0·37)	1·26 (0·31)	1·27 (0·33)		
1 year	1·48 (0·41)	1·48 (0·38)	1·59 (0·41)		
Change	0·20 (0·23)	0·23 (0·23)	0·32 (0·26)	ns	<0·001
TG (mmol/L)					
Baseline	1·41 (0·84)	1·45 (0·88)	1·44 (0·80)		
1 year	1·37 (0·69)	1·42 (0·92)	1·18 (0·60)		
Change	−0·04 (0·68)	−0·03 (0·80)	−0·26 (0·60)	ns	<0·001
Fasting glucose (mmol/L)					
Baseline	5·29 (0·76)	5·37 (0·64)	5·31 (0·71)		
1 year	5·30 (0·93)	5·30 (0·68)	5·20 (0·68)		
Change	0·01 (0·90)	−0·07 (0·62)	−0·11 (0·66)	ns	ns
Fasting insulin (mU/mL)					
Baseline	11·8 (7·7)	12·7 (10·3)	12·7 (10·0)		
1 year	12·7 (9·5)	12·5 (8·2)	11·0 (6·1)		
Change	1·0 (8·7)	−0·3 (10·2)	−1·7 (8·8)	ns	0·002
HOMA-IR (%)					
Baseline	2·8 (2·0)	3·1 (3·2)	3·1 (2·7)		
1 year	3·1 (2·5)	3·0 (2·3)	2·6 (1·7)		
Change	0·3 (2·2)	−0·1 (3·3)	−0·5 (2·4)	ns	0·005

Data are mean (SD). Analyses for total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were done on percentage changes from baseline. SBP=systolic blood pressure. DBP=diastolic blood pressure. ns=not significant.

Table 3: **Changes in selected metabolic and cardiovascular risk factors in patients who completed 1 year follow-up**

Statistical analysis

For the primary endpoint, analysis was done in the ITT population using the last observation carried forward method and presented as mean and SD, unless otherwise stated. An analysis of variance (ANOVA) model, with treatment and randomisation strata as fixed effects, was used, followed by the modified Bonferroni procedure (Hochberg) to account for multiplicity of doses. For secondary endpoints, continuous variables were analysed by means of one-way ANOVA with treatment as fixed effect. Categorical variables were analysed with the χ^2 test. Each rimonabant dose group was compared with the placebo group.

Analysis of covariance (ANCOVA) and/or logistic regression models using weight loss as covariate were applied to investigate whether the observed effects on efficacy endpoints were independent of weight loss as reflected by the last weight measurement. All statistical tests were two-sided at the 5% significance level.

Role of the funding source

The study was designed by the steering committee, composed of the investigators of the RIO programme and a representative from the sponsor. The trial design and follow-up were assessed by the Trial Operational Committee. Data were collected by the pharmaceutical sponsor and were assessed jointly by the authors and the sponsor. The data were interpreted and the manuscript written by the authors. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

309 men and 1198 women were randomised to double-blind treatment. 920 patients (61%) completed the 1-year follow-up: 178 (58·4%) in the placebo group, 379 (62·7%) in the rimonabant 5 mg group, and 363 (60·6%) in the rimonabant 20 mg group (figure 1).

The treatment groups had similar demographic and baseline characteristics (table 1). 346 patients with a BMI of 40 kg/m^2 or greater were enrolled. At baseline, 617 (40·9%) patients had hypertension, 915 (60·8%) had dyslipidaemia, and 615 (41·4%) met the criteria for metabolic syndrome. During the 4-week run-in period, the mean decrease in weight across all groups was 1·9 kg (SD 2·2), with associated reductions of 1·5 cm (3·5) in waist circumference, 0·05 mmol/L (0·66) in triglyceride concentration, and 0·08 mmol/L (0·23) in HDL-cholesterol concentration.

In the ITT population, change in bodyweight from baseline was significantly greater in the rimonabant 5 mg and 20 mg groups than in the placebo group (figure 2A and table 2). Table 3 shows differences between the groups in patients who completed the allocated treatment. Taking into consideration the mean weight loss during the run-in period of 1·9 kg, total cumulative weight loss ranged from 5 kg in the placebo group to more than 10 kg in patients on rimonabant 20 mg. Waist circumference changed significantly from baseline in the rimonabant 5 mg and 20 mg groups (figure 2B, tables 2 and 3).

Placebo-subtracted analysis showed that rimonabant 20 mg was associated with significant (all $p<0·001$) weight loss (mean –4·7 kg [SE 0·4] for ITT and –5·1 kg [0·6] for completers) and reduction in waist circumference (–4·2 cm [0·5] and –4·0 cm [0·6]; data not shown). In the ITT population, a significantly greater proportion of patients in the rimonabant groups achieved weight loss of 5% or greater from baseline compared with the placebo group (figure 3A). The proportion of completers who had 10% or more weight loss was also greater in the rimonabant 20 mg group than in the placebo group, but not different between the

5 mg group and placebo. A similar pattern of results was seen in completers (figure 3B).

In morbidly obese patients (BMI ⩾40 kg/m²), a similar effect on weight loss was recorded compared with the whole study population (data not shown). Results showed no interaction between sex and weight loss: no significant difference in changes was detected between men and women.

Changes in metabolic and cardiovascular risk factors in the ITT population are shown in table 2. In this population, treatment with rimonabant 5 mg and 20 mg increased HDL-cholesterol by 16·2% (SE 0·8; p=0·048 compared with placebo) and 22·3% (0·9; p<0·001), respectively, compared with 13·4% (1·1) in the placebo group (figure 4A). Triglyceride concentrations were reduced by 6·8% (SE 1·5; p<0·0001 *vs* placebo) in the rimonabant 20 mg group, compared with an increase of 5·7% (1·9) in the 5 mg group and 8·3% (2·6) in the placebo group, in the ITT population (figure 4B). Results in completers are presented in table 3.

Logistic regression models and/or ANCOVA using weight loss as a covariate were applied to assess whether the effects of rimonabant 20 mg on both HDL-cholesterol and triglyceride at 12 months were partly independent of weight loss as reflected by the last weight measurement. The weight-loss-adjusted difference in HDL-cholesterol (expressed as the percentage change from baseline) between the placebo and rimonabant 20 mg groups was 3·6% (p=0·01 *vs* placebo), compared with an unadjusted difference of 8·9% (p<0·001 *vs* placebo); this value would translate to about 60% of the increase in HDL-cholesterol being accounted for by the observed weight loss in the ITT population. Similarly, the weight-loss-adjusted difference in the percentage change in triglyceride concentrations between placebo and rimonabant 20 mg was –8·3% (p=0·006 *vs* placebo) compared with the unadjusted difference of –15·1% (p<0·001 *vs* placebo) in the ITT population, corresponding to about 45% of the reduction being accounted for by the observed weight loss.

A significant decrease in non-HDL-cholesterol was observed in the rimonabant 20 mg group compared with placebo (4·3% [SD 16·1] *vs* –0·2% [18·3]; p<0·001) in the ITT population; no difference was noted between the rimonabant 5 mg and placebo groups. Changes in LDL-cholesterol and total cholesterol were not significantly different between the rimonabant and placebo groups.

In the ITT population, 1-year treatment with rimonabant 20 mg resulted in a significant reduction in fasting plasma glucose, compared with the placebo group (table 2). A similar pattern was observed for insulin concentration. A decrease from baseline in HOMA-IR was seen in the rimonabant 20 mg, whereas this index increased in the placebo group. No significant differences in fasting plasma glucose, fasting insulin, or HOMA-IR, were noted between the rimonabant 5 mg group and placebo. Results for completers are presented in table 3. The proportion of patients with impaired glucose tolerance or diabetes during the oral glucose tolerance test at baseline who improved their glucose tolerance status was not different between groups. The 2-h post-load glucose concentrations were not statistically significant between groups. However, rimonabant 20 mg was associated with a significant reduction in 2-h insulin (–11·0 μU/mL [SD 40·1] from baseline *vs* –2·3 μU/mL [38·5] with placebo; p=0·019), a marker of insulin resistance. There were no significant differences in post-load insulin concentrations between rimonabant 5 mg and placebo.

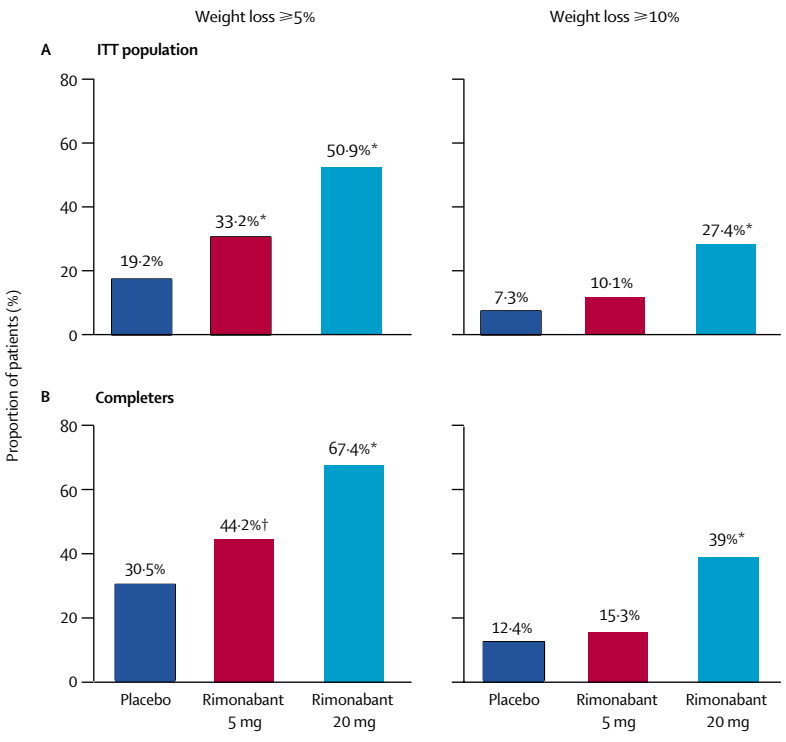


Figure 3: **Proportion of patients who lost ⩾5% and ⩾10% of baseline weight at 1 year**
*p<0·001 *vs* placebo. †p=0·002 *vs* placebo.

Overall, there were no interactions between sex and observed weight loss, changes in metabolic parameters, or reduction in waist circumference. Although the systolic and diastolic blood pressure were slightly reduced after 1 year of rimonabant 20 mg treatment, the changes were not significantly different from placebo.

The proportion of patients who fulfilled the criteria for the metabolic syndrome in the ITT and completer populations is shown in table 4. At 1 year from baseline, the proportion had decreased significantly more in the rimonabant 20 mg group than in the placebo group.

The frequency of adverse events was slightly higher in the rimonabant 20 mg group than in the rimonabant 5 mg and placebo groups. Table 5 provides an analysis of all the adverse events occurring in at least 5% of patients in any group. The most common adverse events occurring with rimonabant were: nausea, dizziness,

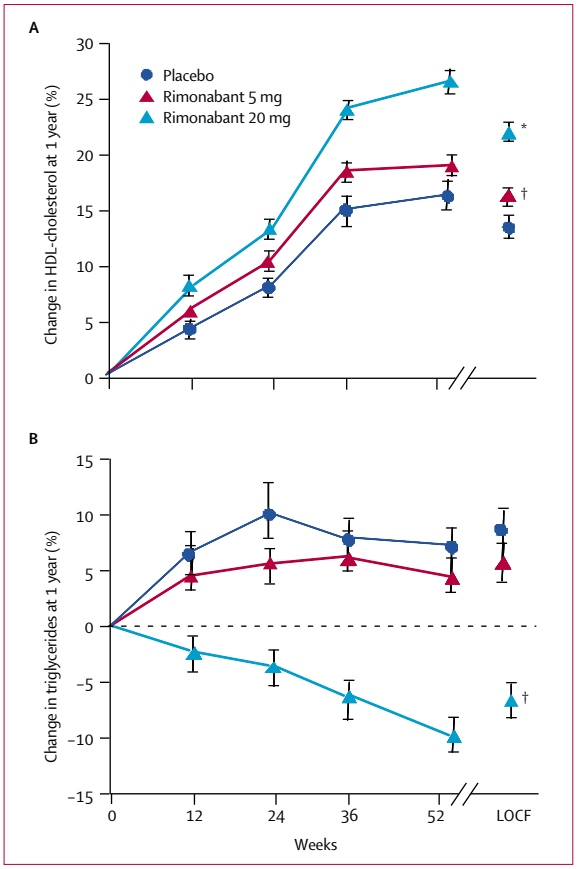


Figure 4: **Mean percentage change from baseline in HDL-cholesterol (A) and triglycerides (B)**
Data are mean (SE) values for patients completing each scheduled visit, and LOCF (values for the full ITT population with the last observations carried forward). *p<0·001 *vs* placebo. †p=0·002 *vs* placebo.

arthralgia and diarrhoea, some patients exhibiting a higher incidence with rimonabant 20 mg. These events, however, were for the most part, mild to moderate in intensity and considered to be transient, based on the occurrence mainly during the first months of the study. There was more headache, fatigue, and upper respiratory infection in the placebo group.

Similar frequencies of serious adverse events were reported in all groups: except for psychiatric disorders, no differences between the treatment groups were observed (tables 5 and 6). Two deaths were reported: one in the placebo group (haemorrhagic cerebrovascular accident, about 2·5 months after randomisation, in a 63-year-old woman treated with phenprocoumon for an aortic valve prothesis), and one in the rimonabant 20 mg group (diagnosis of uterine adenocarcinoma 2 months after randomisation in a 55-year-old woman, resulting in death 3 weeks later due to complications).

The discontinuation rate was similar between the groups, with more withdrawals due to adverse events in the rimonabant 20 mg group and a higher rate of discontinuation due to lack of effect in the placebo group (figure 1). The most common adverse events leading to study discontinuation were depressed mood disorders in all treatment groups; discontinuations due to nausea, vomiting, diarrhoea, headache, dizziness, and anxiety were more frequent in the rimonabant 20 mg group than in the other groups (table 7).

After 1 year, there were no significant changes in the HAD scale subscores for depression (placebo 2·7 [SD 2·9], rimonabant 5 mg 2·7 [2·7], and rimonabant 20 mg 3·4 [3·4]) or anxiety (4·4 [4·0], 4·5 [3·7], and 5·6 [4·1]). Similar proportions of patients with post-baseline depression subscores of 11 or greater were noted in the placebo (23, 8·5%), rimonabant 5 mg (40, 7·5%), and rimonabant 20 mg groups (41, 7·9%). No specific changes in laboratory parameters for haematology or kidney and liver functions were reported. No effect of rimonabant on blood pressure was noted (tables 2 and 3). Mean heart rate remained unchanged from baseline with rimonabant 20 mg, and QTcF decreased by 5·7 msec (SD 16·3) in the placebo group and 3·6 msec (16·9) in the rimonabant 20 mg group.

	Placebo (%)	Rimonabant 5 mg (%)	Rimonabant 20 mg (%)
ITT			
Baseline	108 of 271 (39·9%)	228 of 553 (41·2%)	228 of 540 (42·2%)
1 year	85 of 271 (31·4%)	158 of 553 (28·6%)	106 of 540 (19·6%)*
Change from baseline (%)	21·3%	30·6%	53·6%*
Completers			
Baseline	65 of 167 (38·9%)	155 of 366 (42·3%)	159 of 354 (44·9%)
1 year	43 of 167 (25·7%)	101 of 366 (27·6%)	56 of 354 (15·8%)*
Change from baseline (%)	33·9%	34·8%	64·8%*

*p<0·001 rimonabant 20 mg *vs* placebo.

Table 4: **Prevalence of the metabolic syndrome in the ITT and completer populations at baseline and after 1 year of treatment**

Discussion

In this study, treatment with rimonabant over 1 year led to sustained, clinically meaningful weight loss, reduction in waist circumference, and associated improvements in several cardiovascular and metabolic risk factors, including HDL-cholesterol and triglyceride concentrations, HOMA-IR, and prevalence of the metabolic syndrome. About half of the effect of rimonabant on HDL-cholesterol and triglycerides was independent of weight loss. Despite a significant effect on bodyweight, rimonabant 5 mg had an effect of limited clinical interest on metabolic variables. More than 67% of patients who completed treatment with rimonabant 20 mg achieved 5% or more weight loss, and 39% achieved 10% or more weight loss; the target of 5–10% weight loss, which is judged to be standard in the field of conventional obesity treatment, could be achieved.[20,21] The pattern of weight loss observed in this study with rimonabant appears to be sustained up to 36–40 weeks. How this finding would translate into prolonged weight loss in clinical practice has to be determined. The decrease in waist circumference, a measure of abdominal obesity, is known to be

associated with improvements in cardiovascular disease risk factors,[22,23] including atherothrombotic and pro-inflammatory metabolic abnormalities.[24] The weight loss observed in 39% of patients treated with rimonabant 20 mg was associated with a concomitant reduction in waist circumference by about 9 cm, a value that could be associated with a 30% decrease in intra-abdominal adiposity.[24]

Rimonabant treatment was associated with significant improvements in lipid and glycaemic variables. Importantly, the improvements in HDL-cholesterol and triglycerides observed in this study could not be fully explained by the observed weight loss alone; this statement is supported by the changes over time in these metabolic variables compared with bodyweight. The marked increase of HDL-cholesterol among placebo-treated patients can partly be explained by the fact that, during the run-in period, HDL-cholesterol decreased by about 6% (data not shown) as a logical consequence of the negative energy balance during that period. Irrespective of this effect, the placebo-subtracted benefit in HDL-cholesterol increase with rimonabant reached about 10%. In view of the knowledge that a 1% increase in HDL-cholesterol might lead to a 2% reduction in cardiovascular risk, these findings seem to be promising.[25]

The endocannabinoid system is a neuromodulatory system that plays a role in many physiological processes, including the regulation of food intake and energy homoeostasis.[5] Over the past decade, understanding of endocannabinoid biology has progressed substantially with the identification of two G protein-coupled cannabinoid receptors, CB_1 and CB_2,[26,27] and their endogenous ligands. CB_1 receptors are located in the central nervous system and in various peripheral tissues.[28] CB_2 receptors are located in the immune system and do not seem to have a role in energy homoeostasis.[29] Rimonabant is a selective CB_1 blocker that suppresses tonic endogenous activation of the endocannabinoid system centrally[4,6] and peripherally[8,30] (figure 5).

Rimonabant reduces the excessive consumption of palatable food or drinks in rats and marmosets.[31,32] The mechanism by which rimonabant regulates food intake is probably centrally mediated,[15] but recent results suggest an additional peripheral action. Indeed, endocannabinoids derived from the gastrointestinal tract appear to be able to modulate feeding behaviour by acting on CB_1 receptors located on capsaicin-sensitive sensory terminals.[11] In diet-induced obese mice, rimonabant treatment leads to a marked and sustained reduction of bodyweight and adiposity that could not be explained by the transient reduction of food intake observed. When compared with food restriction in a pair-feeding protocol, rimonabant treatment induced a greater bodyweight loss in diet-induced obese mice,[10] indicating that the effects of rimonabant on bodyweight are partly independent of food intake. It seems likely that CB_1 receptors expressed on adipocytes might be one of

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Any adverse events	257 (84·3%)	498 (82·6%)	522 (87·1%)
Nasopharharyngitis	48 (15·7%)	87 (14·4%)	93 (15·5%)
Influenza	32 (10·5%)	51 (8·5%)	54 (9·0%)
Gastroenteritis	24 (7·9%)	40 (6·6%)	51 (8·5%)
Upper respiratory tract infection	23 (7·5%)	43 (7·1%)	33 (5·5%)
Bronchitis	16 (5·2%)	34 (5·6%)	34 (5·7%)
Sinusitis	17 (5·6%)	27 (4·5%)	26 (4·3%)
Headache	41 (13·4%)	58 (9·6%)	59 (9·8%)
Dizziness	15 (4·9%)	42 (7·0%)	52 (8·7%)
Nausea	13 (4·3%)	31 (5·1%)	77 (12·9%)
Diarrhoea	9 (3·0%)	36 (6·0%)	43 (7·2%)
Arthralgia	21 (6·9%)	58 (9·6%)	47 (7·8%)
Back pain	26 (8·5%)	56 (9·3%)	55 (9·2%)
Fatigue	17 (5·6%)	24 (4·0%)	25 (4·2%)

Table 5: **Patients reporting adverse events (≥5% in any treatment group)**

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Any serious adverse event	23 (7·5%)	45 (7·5%)	52 (8·7%)
Respiratory disorders	0	0	2 (0·3%)
Psychiatric disorders	1 (0·3%)	2 (0·3%)	9 (1·5%)
Nervous system disorders	3 (1·0%)	7 (1·2%)	3 (0·5%)
Ear disorders	0	0	1 (0·2%)
Cardiac disorders	0	2 (0·3%)	2 (0·3%)
Vascular disorders	0	2 (0·3%)	3 (0·5%)
Gastrointestinal disorders	3 (1·0%)	3 (0·5%)	2 (0·3%)
Hepatobiliary disorders	3 (1·0%)	5 (0·8%)	1 (0·2%)
Musculoskeletal and connective disorders	6 (2·0%)	13 (2·2%)	10 (1·7%)
Renal and urinary disorders	0	2 (0·3%)	2 (0·3%)
Reproductive system and breast disorders	1 (0·3%)	2 (0·3%)	3 (0·5%)
Investigations	1 (0·3%)	0	1 (0·2%)
Injury, poisoning, and procedure complications	4 (1·3%)	5 (0·8%)	4 (0·7%)
Neoplasms: benign, malignant, and unspecified	2 (0·7%)	5 (0·8%)	7 (1·2%)
General disorders	0	0	1 (0·2%)

Data are proportions of patients with at least one serious event.

Table 6: **Serious adverse events by system organ class during the double-blind period of the trial**

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Any adverse event leading to discontinuation	28 (9·2%)	50 (8·3%)	87 (14·5%)
Psychiatric disorders	16 (5·2%)	18 (3·0%)	42 (7·0%)
Depressed mood disorders	9 (3·0%)	14 (2·3%)	22 (3·7%)
Anxiety	1 (0·3%)	0	6 (1·0%)
Agitation	2 (0·7%)	0	3 (0·5%)
Sleep disorders	0	2 (0·3%)	1 (0·2%)
Nervous system disorders	2 (0·7%)	8 (1·3%)	10 (1·7%)
Headache	0	2 (0·3%)	4 (0·7%)
Dizziness	0	2 (0·3%)	2 (0·3%)
Hypoaesthesia	0	0	2 (0·3%)
Gastrointestinal disorders	0	5 (0·8%)	21 (3·5%)
Nausea	0	1 (0·2%)	14 (2·3%)
Vomiting	0	0	4 (0·7%)
Diarrhoea	0	0	3 (0·5%)
Dyspepsia	0	0	2 (0·3%)
Flatulence	0	2 (0·3%)	0
Cardiac disorders	3 (1·0%)	2 (0·3%)	5 (0·8%)
Palpitations	1 (0·3%)	0	2 (0·3%)

According to the Medical Dictionary for Regulatory Activities in at least two patients in any treatment group (one patient may report several events). Only main system organ classes are presented.

Table 7: **Patients reporting adverse events leading to discontinuation**

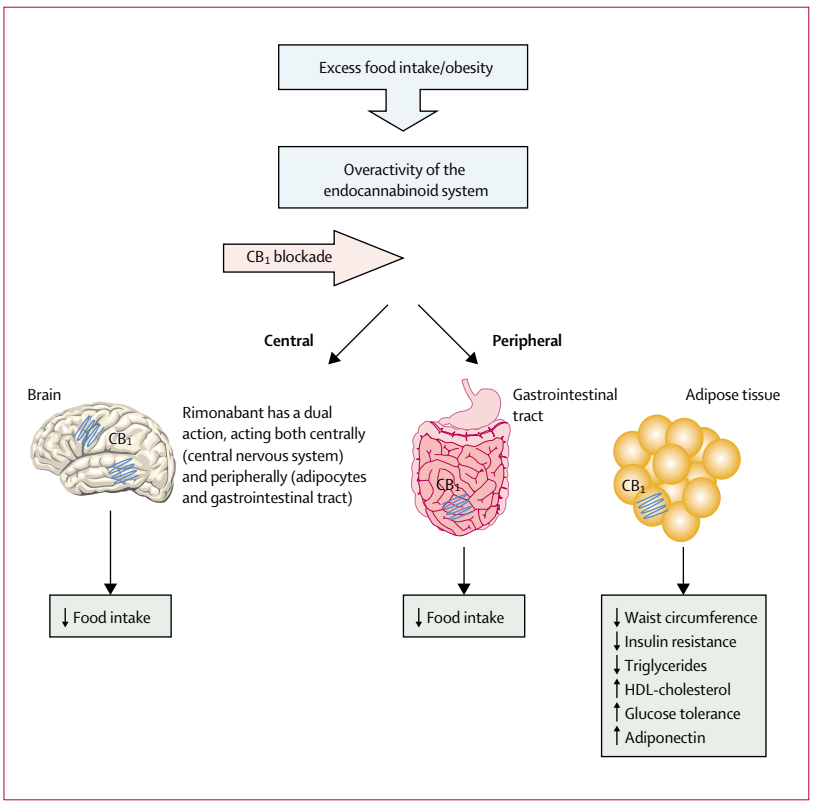


Figure 5: **Hypothetical model of role of central and peripheral components of endocannabinoid system in regulation of food intake and peripheral metabolism**
CB_1 receptors are enriched in regions of the brain and in gastrointestinal system implicated in the regulation of food intake, and in adipose tissue. CB_1 receptor blockade might contribute to decreased food intake and exert direct metabolic effects.

the effectors of the possible peripheral metabolic action of rimonabant.

A possible explanation for the potential weight-independent effect of rimonabant on HDL-cholesterol and triglycerides might be related to the observation that rimonabant enhances the mRNA expression of adiponectin, an adipokine secreted by fat cells and reported to have a role in the regulation of hyperglycaemia, hyperinsulinaemia, and fatty acid oxidation,[33–36] at the peripheral adipocyte level.[8] Thus, improved fat-cell function may be postulated as a key peripheral effect of rimonabant leading to bodyweight reduction and improvement in metabolic parameters, including lipids and beneficial changes in adiponectin and C-reactive protein. Further studies of the in-vivo effects of the increased adiponectin production induced by rimonabant treatment are needed to elucidate possible metabolic effects of rimonabant in adipose tissue.

Rimonabant treatment was well tolerated during this trial, with a similar overall drop-out rate in all treatment groups. The most common adverse events experienced with rimonabant 20 mg, such as nausea and diarrhoea, were found to be mild and generally occurred in the first few months of the treatment. Gastrointestinal side-effects might be explained by the mechanism of action of the drug, since it is known that CB_1 receptors are present in the gut and likely to be involved in gastrointestinal motility. Serious adverse events did not seem to occur more frequently in the patients treated with rimonabant than in those on placebo. Mood disorders were more frequent in the rimonabant 20 mg treatment group than in the other groups, but the discontinuation rate due to this adverse event was similar between rimonabant 20 mg and placebo in this study.

The RIO-Europe trial was designed to reflect a real-life clinical setting in which we assessed parameters indicative of the metabolic syndrome and relevant clinical endpoints, such as waist circumference, in patients with a range of pre-existing risk factors. The 1-year results emphasise that blockade of the CB_1 receptor clearly targets several causes of cardiovascular risk, including obesity and the metabolic syndrome, along with its associated parameters such as waist circumference, HDL-cholesterol, and insulin resistance. The prevalence of the metabolic syndrome, compared with baseline, was reduced by more than half in the ITT population and by almost two-thirds in completers. There has been an increased awareness of the importance of this syndrome and its relation to cardiovascular disease in recent years. The large number of patients treated with CB_1 blockade who achieved the 10% target for weight loss or had a marked improvement in the top risk factors established by the world-wide INTERHEART study,[37] suggests that rimonabant can be considered as a valuable adjunct therapy for weight and waist reduction in patients at high cardiovascular risk.

The finding of a significant reduction in the incidence of the metabolic syndrome after 1 year of treatment with rimonabant 20 mg could have further implications, since the metabolic syndrome has been shown to be an important predictor of the development of type 2 diabetes and coronary heart disease.[38,39] However, the long-term benefits of weight loss and treatment of the metabolic syndrome on the prevention of cardiovascular events and mortality have yet to be confirmed by long-term outcomes studies.

In conclusion, the results of the RIO-Europe trial indicate that modulating the activity of the endocannabinoid system by blocking its CB_1 receptors holds therapeutic promise as an approach to the treatment of obesity and associated risk factors. Treatment with rimonabant was associated with clinically meaningful weight loss and additional improvements in waist circumference, lipid concentrations, and insulin resistance, and had a favourable safety profile.

Contributors

L Van Gaal and A J Scheen were involved in the study design and study follow-up as members of the RIO Operational Committee. Data and final analysis were reviewed and validated by all authors, who then wrote the manuscript. L Van Gaal had full unrestricted access to the complete set of data and wrote the initial draft of the paper. All the named authors participated in the study and contributed to interpretation of data and

revision of the manuscript. The final version was written by L Van Gaal and A J Scheen, and was seen and approved by all authors.

RIO-Europe Study Group

Belgium: J C Daubresse, F Duyck, M Kutnowski, A Scheen, L Van Gaal, B Velckeniers. Finland: I Kantola, L Niskanen, A Rissanen, J Salmi, J Salveto, M Savolainen. Germany: HG Damman, M Derwahl, S Jacob, A Pfeiffer, J Schulze, M Weck. France: M Farnier, M Krempf, P Ritz, M Romom, D Sacareau, C Simon, D Taminau, P Valensi, JY Vogel, O Ziegler. Netherlands: A Deijl, H Emanuels, G de Groot, J Jonker, H Koppeschaar, Y Koster, L Matthus-Vliegen, U Mulder, D Ramautarsing, L de Schipper, P A Top. Sweden: S Rossner. USA: S A Bart, S A Cohen, J E Ervin, H F Farmer, D L Fried, H L Geisberg, S Gordon, C Griffin, W S Holt, J L Kirstein, W E Larson, T Littlejohn, C Monder, D J Morin, D Orchard, D N Pate, J Raese, E Spiotta, M W Warren, J Wolfram.

Conflict of interest statement

LVG, AMR, SR, AJS, and OZ have received travel awards and honoraria from Sanofi-Aventis for the purposes of attending RIO-Europe scientific committee meetings or presenting RIO-Europe trial results.

Acknowledgments

The study was funded by Sanofi-Aventis.

References

1 James PT, Rigby N, Leach R. The obesity epidemic, metabolic syndrome and future prevention strategies. *Eur J Cardiovasc Prev Rehabil* 2004; **11:** 3–8.

2 York DA, Rossner S, Caterson I, et al. American Heart Association. Prevention conference VII: obesity, a worldwide epidemic related to heart disease and stroke: Group I: worldwide demographics of obesity. *Circulation* 2004; **110:** e463–70.

3 WHO. Integrated management of cardiovascular risk: report of a WHO meeting. Geneva; World Health Organisation, 2002.

4 Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003; **112:** 423–31.

5 Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. *Nat Rev Drug Discov* 2004; **3:** 771–84.

6 Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 2001; **410:** 822–25.

7 Croci T, Manara L, Aureggi G, et al. In vitro functional evidence of neuronal cannabinoid CB1 receptors in human ileum. *Br J Pharmacol* 1998; **125:** 1393–95.

8 Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* 2003; **63:** 908–14.

9 Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology* 2004; **47** (suppl 1)**:** 345–58.

10 Ravinet Trillou C, Arnone M, Delgorge C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol* 2003; **284:** R345–53.

11 Gomez R, Navarro M, Ferrer B, et al. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *J Neurosci* 2002; **22:** 9612–17.

12 Kirkham TC. Endogenous cannabinoids: a new target in the treatment of obesity. *Am J Physiol Regul Integr Comp Physiol* 2003; **284:** R343–44.

13 Horvath TL. Endocannabinoids and the regulation of body fat: the smoke is clearing. *J Clin Invest* 2003; **112:** 323–26.

14 Kunos G, Batkai S. Novel physiologic functions of endocannabinoids as revealed through the use of mutant mice. *Neurochem Res* 2001; **26:** 1015–21.

15 Cota D, Marsicano G, Lutz B, et al. Endogenous cannabinoid system as a modulator of food intake. *Int J Obes Relat Metab Disord* 2003; **27:** 289–301.

16 Laboratory Test Handbook. 4th edn. Hudson: Lexi-Comp, 1996.

17 Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106:** 3143–421.

18 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28:** 412–19.

19 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–70.

20 Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992; **16:** 397–415.

21 Van Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord* 1997; **21** (suppl 1)**:** S5–9.

22 Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr* 2002; **76:** 743–49.

23 Janssen I, Katzmarzyk P, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; **79:** 379–84.

24 Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001; **322:** 716–20.

25 Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989; **79:** 8–15.

26 Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990; **346:** 561–64.

27 Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993; **365:** 61–65.

28 Howlett AC. The cannabinoid receptors. *Prostaglandins Other Lipid Mediat* 2002; **68–69:** 619–31.

29 Petrocellis LD, Cascio MG, Marzo VD. The endocannabinoid system: a general view and latest additions. *Br J Pharmacol* 2004; **141:** 765–74.

30 Liu Y, Connoley I, Wilson C, Stock M. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lepob/Lepob mice. *Int J Obes Relat Metab Disord* 2004; **29:** 183–87.

31 Arnone M, Maruani J, Chaperon F, et al. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. *Psychopharmacology (Berl)* 1997; **132:** 104–06.

32 Simiand J, Keane M, Keane PE, Soubrie P. SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. *Behav Pharmacol* 1998; **9:** 179–81.

33 Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001; **7:** 947–53.

34 Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J Clin Invest* 2001; **108:** 1875–81.

35 Fruebis J, Tsao TS, Javorschi S, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 2001; **98:** 2005–10.

36 Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; **7:** 941–46.

37 Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364:** 937–52.

38 Meigs JB, Wilson PW, Nathan DM, D'Agostino RB Sr, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 2003; **52:** 2160–67.

39 Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003; **52:** 1210–14.

Exhibit B

NYPL RESEARCH LIBRARIES
3 3433 06300519 9
DELIVERY DESK & JSP 90-196 SIBL
The New England journal of medicine.
v. 353
no. 20
Nov 17, 2005
Latest 3 issues also
NM

The JOURNAL OF MEDICINE

VOL. 353 NO. 20

ESTABLISHED IN 1812 NOVEMBER 17, 2005 WWW.NEJM.ORG

2110 THIS WEEK IN THE JOURNAL

PERSPECTIVE

2101 The Promise of Global Cervical-Cancer Prevention M. Schiffman and P.E. Castle

2104 Genetic Diversity in Melanoma P.S. Meltzer

2107 So Where's My Medal? P. Klass

ORIGINAL ARTICLES

2111 Randomized Trial of Lifestyle Modification and Pharmacotherapy for Obesity
T.A. Wadden and Others

2121 Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia
J.-P. Després and Others

2135 Distinct Sets of Genetic Alterations in Melanoma
J.A. Curtin and Others

2148 Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension
N. Galiè and Others

SPECIAL ARTICLE

2158 Cost-Effectiveness of Cervical-Cancer Screening in Five Developing Countries
S.J. Goldie and Others

CLINICAL PRACTICE

2169 Long-Acting Methods of Contraception
H.B. Peterson and K.M. Curtis

IMAGES IN CLINICAL MEDICINE

2176 Lentigo Maligna
B. Noel and N. Kunzle

e18 Pulmonary Sequestration
A. Platon and P.-A. Poletti

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

2177 A Woman with Breast Cancer and Isolated Tumor Cells in a Sentinel Lymph Node
N.E. Davidson and Others

EDITORIAL

2187 Pharmacotherapy for Obesity — Promise and Uncertainty
S.Z. Yanovski

2190 CORRESPONDENCE
Erythropoietin as a Retinal Angiogenic Factor
Bone Marrow Micrometastases in Breast Cancer
Hyperinsulinemic Hypoglycemia with Nesidioblastosis after Gastric-Bypass Surgery
Lung-Cancer Screening
Case 23-2005: A Man with a Mass in the Liver
Obesity and Mortality

2200 BOOK REVIEWS

2204 NOTICES

2205 CONTINUING MEDICAL EDUCATION

Owned & published by the MASSACHUSETTS MEDICAL SOCIETY © 2005. All rights reserved. ISSN 0028-4793.

YOUR CUSTOMER NUMBER: 000571739

#BXNBVJG **********AUTO**5-DIGIT 10163
000571739/6 # 20051229 20051117 0055 119
NEW YORK PUB LIB 8067
SCIENCE IND & BUS LIB/ GRAND CENTRAL STA 1
PO BOX 2233
NEW YORK NY 10163-2233

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia

Jean-Pierre Després, Ph.D., Alain Golay, M.D., and Lars Sjöström, M.D., Ph.D., for the Rimonabant in Obesity–Lipids Study Group*

ABSTRACT

BACKGROUND

Rimonabant, a selective cannabinoid-1 receptor (CB_1) blocker, has been shown to reduce body weight and improve cardiovascular risk factors in obese patients. The Rimonabant in Obesity–Lipids (RIO-Lipids) study examined the effects of rimonabant on metabolic risk factors, including adiponectin levels, in high-risk patients who are overweight or obese and have dyslipidemia.

METHODS

We randomly assigned 1036 overweight or obese patients (body-mass index [the weight in kilograms divided by the square of the height in meters], 27 to 40) with untreated dyslipidemia (triglyceride levels >1.69 to 7.90 mmol per liter, or a ratio of cholesterol to high-density lipoprotein [HDL] cholesterol of >4.5 among women and >5 among men) to double-blinded therapy with either placebo or rimonabant at a dose of 5 mg or 20 mg daily for 12 months in addition to a hypocaloric diet.

RESULTS

The rates of completion of the study were 62.6 percent, 60.3 percent, and 63.9 percent in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively. The most frequent adverse events resulting in discontinuation of the drug were depression, anxiety, and nausea. As compared with placebo, rimonabant at a dose of 20 mg was associated with a significant ($P<0.001$) mean weight loss (repeated-measures method, −6.7±0.5 kg, and last-observation-carried-forward analyses, −5.4±0.4 kg), reduction in waist circumference (repeated-measures method, −5.8±0.5 cm, and last-observation-carried-forward analyses, −4.7±0.5 cm), increase in HDL cholesterol (repeated-measures method, +10.0±1.6 percent, and last-observation-carried-forward analyses, +8.1±1.5 percent), and reduction in triglycerides (repeated-measures method, −13.0±3.5 percent, and last-observation-carried-forward analyses, −12.4±3.2 percent). Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels (repeated-measures method, 57.7 percent, and last-observation-carried-forward analyses, 46.2 percent; $P<0.001$), for a change that was partly independent of weight loss alone.

CONCLUSIONS

Selective CB_1-receptor blockade with rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.

From the Quebec Heart Institute, Laval Hospital Research Center, and the Division of Kinesiology, Department of Social and Preventive Medicine, Laval University, Ste.-Foy, Que., Canada (J.-P.D.); the Service of Therapeutic Education for Chronic Diseases, University Hospital Geneva, Geneva (A.G.); and the Department of Body Composition and Metabolism, Sahlgrenska University Hospital, Göteborg, Sweden (L.S.). Address reprint requests to Dr. Després at the Quebec Heart Institute, Laval Hospital Research Center, Pavilion Marguerite-D'Youville, 4th Fl., 2725 Chemin Ste.-Foy, Ste.-Foy, QC G1V 4G5, Canada, or at jean-pierre.despres@crhl.ulaval.ca.

*The investigators and coinvestigators participating in the Rimonabant in Obesity–Lipids (RIO-Lipids) Study Group are listed in the Appendix.

N Engl J Med 2005;353:2121-34.

Copyright © 2005 Massachusetts Medical Society.

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

The epidemic of obesity in developed countries illustrates the inability of homeostatic mechanisms to offset a sedentary lifestyle[1] and almost unlimited access to processed, energy-dense foods of poor nutritional value. Although modification of nutritional and physical-activity habits is the cornerstone of therapy for obesity, pharmacotherapy focusing on improvement of the metabolic risk profile in abdominally obese patients who are at high risk of diabetes and cardiovascular disease may be required. The newly discovered endocannabinoid (EC) system and cannabinoid CB_1 receptor,[2] with their reported roles in the regulation of energy balance and body composition, offer a new target to induce weight loss and improve the metabolism of carbohydrates and lipids.[2-4]

The EC system consists of a family of locally produced, short-lived, endogenous, phospholipid-derived agonists (endocannabinoids)[5,6] and the $G_{I/O}$-protein–coupled CB_1 receptor[7] that they activate. CB_1 receptors are expressed predominantly in several areas of the brain and in peripheral organs, including the autonomic nervous system, liver, muscle, gastrointestinal tract, and adipose tissue.[2] Administration of the first endocannabinoid discovered, anandamide, in the hypothalamus or of 2-arachidonoyl-glycerol in the nucleus accumbens can provoke food intake in satiated rodents.[8,9] As compared with wild-type animals, CB_1-knockout mice have leaner body composition, but this lean phenotype is not fully explained by changes in food intake.[3]

Stimulation of the CB_1 receptors in fat cells promotes lipogenesis and inhibits the production of adiponectin,[3,10] a cytokine derived from adipose tissue that has potentially important antidiabetic and antiatherosclerotic properties.[11] Rimonabant, the first specific CB_1-receptor blocker to enter clinical development, has been shown to reduce food intake and body weight in treated animals and to alter metabolic activity in adipose tissue[12] while inducing the expression of the adiponectin gene.[13] The results of a phase 3 study involving obese patients (Rimonabant in Obesity–Europe [RIO-Europe] study) showed that rimonabant induces significant weight loss and improves metabolic risk factors for diabetes and cardiovascular disease.[14] However, the patients enrolled in the study were selected only on the basis of excess weight. Therefore, we examined the effects of rimonabant in persons at higher risk of cardiovascular disease, such as patients with dyslipidemia who were overweight or obese. Also, since only traditional risk factors for cardiovascular disease were measured in the RIO-Europe study, we explored the effect of rimonabant on other key metabolic risk markers for cardiovascular disease such as the size of particles of low-density lipoprotein (LDL) and the plasma levels of C-reactive protein and adiponectin.

METHODS

STUDY DESIGN

The primary objective of the study was to assess the effect of 12 months of randomized, double-blind treatment with rimonabant at a dose of 5 mg or 20 mg, as compared with placebo, in addition to a hypocaloric diet (a deficit of 600 kcal per day in relation to the calculated daily intake to maintain body weight), on the loss of body weight in patients who are overweight or obese (body-mass index [BMI], 27 to 40, with BMI defined as the weight in kilograms divided by the square of the height in meters), have untreated dyslipidemia, and do not have diabetes. Secondary measures included changes from baseline (randomization) in levels of high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and insulin during an oral glucose-tolerance test and the prevalence of the metabolic syndrome (according to the criteria of the third report of the National Cholesterol Education Program Adult Treatment Panel [NCEP-ATPIII]).[15] Additional efficacy measures included waist circumference, leptin and adiponectin levels, and relevant biochemical cardiovascular risk markers. The safety assessment included standard adverse-event reporting, vital signs, the QT interval corrected for heart rate (QTc), and anxiety and depression according to the hospital anxiety and depression scales.[14,16] The range of scores for each scale is 0 to 21, with higher scores indicating a worse condition. Data were gathered by the sponsor (Sanofi Aventis) and were analyzed jointly by the authors and the sponsor. The data analysis and the final analyses were reviewed and validated by the authors, who then wrote the manuscript.

The study was conducted between September 2001 and November 2003 and was in compliance with the Helsinki Declaration. It was conducted at 67 sites in eight countries, with an independent, unblinded data safety monitoring board comprising five permanent members. At each meeting of the data safety monitoring board, it was mandatory to have at least three permanent independent mem-

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

bers, including a clinician, a safety expert, and a statistician. All patients gave written informed consent for participation in the study.

Inclusion criteria were age of 18 to 70 years; BMI of 27 to 40; fasting plasma triglyceride levels of 1.7 to 7.9 mmol per liter (150 to 700 mg per deciliter), a ratio of total cholesterol to HDL cholesterol higher than 5 (among men) and higher than 4.5 (among women), or both; and variation in body weight within the previous three months of less than 5 kg. Exclusion criteria were a history of pharmacologic treatment for dyslipidemia within six weeks before screening, pharmacologic treatment for weight loss within three months before screening, or treatment with a very-low-calorie diet within six months before screening; diabetes mellitus (type 1 or 2); clinically significant findings indicating cardiovascular, endocrine, pulmonary, neurologic, psychiatric, gastrointestinal, hepatic, hematologic, renal, or dermatologic disease; a positive result on a test for hepatitis B surface antigen, hepatitis C antibody, or both; an abnormal thyrotropin level (greater than the upper limit of the normal range or less than the lower limit of the normal range); one or more of the following: levels of alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the upper limit of the normal range; hemoglobin levels less than 11 g per deciliter, neutrophil levels less than 1500 per cubic millimeter, platelet levels of less than 100,000 per cubic millimeter, and a creatinine level greater than 150 μmol per liter (1.7 mg per deciliter); a history of marijuana or hashish use; severe depression (depression requiring hospitalization or indicated by a suicide attempt); and treatment for epilepsy, an eating disorder, or a malignant disease except basal-cell skin cancers (within five years). Other grounds for exclusion included systolic or diastolic blood pressure at screening that was higher than 165 or 105 mm Hg, respectively; pregnancy or lactation; or less than 80 percent compliance with a hypocaloric diet and placebo during the post-screening four-week, single-blind run-in period.[14]

After enrollment, patients were stratified according to baseline triglyceride levels (>4.5 vs. ≤4.5 mmol per liter [400 mg per deciliter]) and weight loss during the run-in period (>2 vs. ≤2 kg) and assigned to double-blind therapy, receiving placebo or rimonabant at a dose of 5 mg or 20 mg in a ratio of 1:1:1. Follow-up visits with a consulting dietitian occurred every 2 weeks for the first two visits and monthly thereafter for 12 months; standardized assessments of body weight, blood pressure, waist circumference, smoking status, and concomitant medications were performed at each visit. Patients were not eligible if they had recently (within the past six months) quit smoking or were considering quitting. Patients who had undergone randomization were not allowed to change smoking status during the study, and smokers who quit during the study period were ruled out because of the known effects of smoking cessation on body weight.

ASSAYS

Standard laboratory tests were performed by ICON Laboratories (at sites in Farmingdale, New York, and Dublin). The peak size of LDL particles and the proportion of small (<255 Å) LDL particles were determined by means of nondenaturing 2 to 16 percent polyacrylamide-gradient–gel electrophoresis.[17] Apolipoprotein B and apolipoprotein A-I were quantified by nephelometry. Serum C-reactive protein levels were measured by immunoturbidimetric assay, glucose with the use of the hexokinase method, insulin by immunometric assay, leptin by radioimmunoassay,[18] and adiponectin by an enzyme-linked immunosorbent assay (B-Bridge International). A 75-g oral glucose-tolerance test was performed in the morning after an overnight fast, and glucose and insulin areas under the curve (AUCs) were calculated with the use of the trapezoid method.

STATISTICAL ANALYSIS

All statistical tests were two-sided, with an alpha level of 0.05. The prespecified analysis of the primary end point (change in weight from baseline at the last observation carried forward) was conducted with the use of analysis of variance with the modified Bonferroni procedure (Hochberg) for adjustment for multiple comparisons. The analysis of variance included terms for treatment and randomization subgroup. Because this analysis ruled out scheduled measurements collected during the study, a post-hoc repeated-measures approach was performed for changes in weight from baseline, which provided a better estimate of the true effect of the study drug. The repeated-measures model included the fixed effects (randomization subgroup, treatment, day [number of days after randomization], and treatment-by-day interaction) and a random effect (the patient). Similar methods were used for the analysis of other efficacy end points.

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 1. Patients' Assignments, Values at Screening, and Baseline Efficacy and Safety Values.*

Variable	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Patients' assignment — no. (%)			
Randomly assigned and exposed to medication	342 (100)	345 (100)	346 (100)
Intention-to-treat analysis†	334 (97.7)	340 (98.6)	344 (99.4)
Completed study	214 (62.6)	208 (60.3)	221 (63.9)
Reason for discontinuation	128 (37.4)	137 (39.7)	125 (36.1)
Lack of efficacy	2 (0.6)	4 (1.2)	3 (0.9)
All adverse events	31 (9.1)	29 (8.4)	56 (16.2)
Poor compliance	13 (3.8)	18 (5.2)	13 (3.8)
Patient's request	70 (20.5)	71 (20.6)	42 (12.1)
Lost to follow-up	12 (3.5)	10 (2.9)	8 (2.3)
Other	0	5 (1.4)	3 (0.9)
Screening values			
Sex — %			
Male	42.1	37.7	38.4
Female	57.9	62.3	61.6
Current smoker — %	17.8	16.8	15.3
Age — yr‡	47.0±10.1	48.1±10.2	48.4±10.0
Height — cm	168±9	168±9	167±10
Weight — kg	97.0±15.4	96.0±14.6	95.3±15.1
Body-mass index‡	34.0±3.5	34.1±3.5	33.9±3.3
Triglycerides — mmol/liter‡	2.26±1.61	2.36±1.13	2.42±1.14
Total cholesterol — mmol/liter	6.01±0.86	6.03±0.81	5.91±0.91
HDL cholesterol — mmol/liter	1.15±0.24	1.16±0.25	1.14±0.25
Total cholesterol:HDL cholesterol ratio‡	5.38±1.02	5.37±1.09	5.33±1.09
Baseline efficacy values			
Weight — kg	95.0±15.1	94.2±14.6	93.3±14.8
Waist circumference — cm	105.7±11.4	104.8±10.8	104.7±11.0
Triglycerides — mmol/liter	2.05±1.21	2.10±1.41	2.11±1.15
Total cholesterol — mmol/liter	5.65±0.94	5.63±0.96	5.59±1.00
LDL cholesterol — mmol/liter	3.58±0.78	3.52±0.79	3.46±0.86
Peak size of LDL particles — Å	259.3±5.0	260.0±5.0	259.1±4.8
Proportion of small LDL particles (<255Å) — %	26.2±21.4	25.2±20.2	25.8±21.0
HDL cholesterol — mmol/liter	1.10±0.25	1.10±0.23	1.11±0.24
Total cholesterol:HDL cholesterol ratio	5.31±1.13	5.29±1.11	5.19±1.10
LDL cholesterol:HDL cholesterol ratio	3.36±0.82	3.30±0.83	3.20±0.81
Apolipoprotein B:apolipoprotein A-I ratio§	0.73±0.15	0.73±0.18	0.72±0.16
Fasting glucose — mmol/liter	5.29±0.64	5.33±0.71	5.29±0.59
Fasting insulin — μU/ml	12.8±11.4	13.0±8.0	12.8±12.3
Metabolic syndrome — %	51.9	55.9	52.9
Adiponectin — μg/ml¶	5.7±2.5	5.8±2.9	5.9±2.9
Leptin — ng/ml	18±10	20±12	18±11
C-reactive protein — mg/liter	5.3±5.3	5.2±5.3	5.0±5.0

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 1. (Continued.)

Variable	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Baseline safety values			
Heart rate — bpm	65.7±9.7	65.9±9.8	64.7±8.5
Blood pressure — mm Hg			
Systolic	124.0±13.8	123.8±13.5	124.9±12.7
Diastolic	78.2±8.4	78.1±8.9	78.2±7.7
QTc — msec	402.1±20.2	403.9±19.3	406.5±21.0
Depression‖	3.0±2.7	3.2±3.1	3.0±2.6
Anxiety‖	5.1±3.8	5.6±4.1	5.3±3.3

* Plus–minus values are means ±SD. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, bpm beats per minute, and QTc the QT interval corrected for heart rate. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.
† At least one post-baseline measurement of body weight was required for the analysis.
‡ The category was required according to the entry criteria of the study.
§ Measurements were performed in a subgroup of patients (231, 224, and 237 patients from the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).
¶ Measurements were performed in a subgroup of patients (231, 222, and 238 patients from the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).
‖ The disorder was measured according to the hospital anxiety and depression scales.[14,16] The range of scores for each scale is 0 to 21, with higher scores indicating a worse condition.

Patients were classified as having a response of a 5 percent weight loss if they had a reduction in body weight from baseline at the last observation carried forward of at least 5 percent; the identification of those with a response of a 10 percent weight loss at the last observation carried forward was performed in a similar manner. The incidences of patients who had a weight loss of 5 percent and 10 percent and of those with the metabolic syndrome at the last observation carried forward were analyzed with the use of logistic-regression models. The models for patients who had weight losses of 5 percent and 10 percent included terms for treatment and randomization subgroup, and the model for the metabolic syndrome included terms for treatment and the status of the metabolic syndrome at baseline. Because C-reactive protein values were not normally distributed, nonparametric analyses were substituted for parametric analyses for this specific marker. The effect of rimonabant independent of weight loss was tested with the use of analysis of covariance with weight loss as a covariate. The values in the tables are presented as means ±SD and presented in the figures as means ±SE for the intention-to-treat population.

RESULTS

About 40 percent of the patients in each of the three treatment groups dropped out during the 12-month study, with a higher dropout rate due to adverse events in the group receiving 20 mg of rimonabant and due to patients' requests in the placebo group and the group receiving 5 mg of rimonabant (Table 1). The characteristics of the patients in the three groups were similar both at screening and at baseline, and there were similar improvements during the four-week placebo run-in period in the three groups with regard to all efficacy measures except HDL cholesterol levels, which declined in all three groups (Table 1).

After a weight loss of approximately 2 kg in each group during the run-in period (Table 1), the placebo group had a further decline of 2.3 kg over the next 12 months, as compared with a weight loss of 4.2 kg and 8.6 kg in the group receiving 5 mg of rimonabant and the group receiving 20 mg of rimonabant, respectively (Table 2) ($P<0.001$ for both doses). Weight loss was generally greater among patients who completed the 12-month study. In the overall population, the proportion of patients who

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 2. Changes from Baseline for the Efficacy and Safety End Points in the Intention-to-Treat Population, According to the Repeated-Measures (RM) Method and Last-Observation-Carried-Forward (LOCF) Analyses.*

End Point	Placebo Group	5-mg Rimonabant Group		20-mg Rimonabant Group	
			P Value		P Value
Efficacy end point					
Weight (kg)					
RM	−2.3±5.6	−4.2±5.3	<0.001	−8.6±6.0	<0.001
LOCF	−1.5±5.0	−3.1±4.8	<0.001	−6.9±6.1	<0.001
Waist circumference (cm)					
RM	−3.4±6.0	−4.9±6.2	0.016	−9.1±6.6	<0.001
LOCF	−2.4±5.7	−3.5±6.0	0.029	−7.1±6.8	<0.001
Triglycerides (%)					
RM	−3.6±36.4	0.0±40.5	NS	−15.8±38.0	<0.001
LOCF	−0.2±38.7	+1.2±39.4	NS	−12.6±41.2	<0.001
Total cholesterol (%)					
RM	+1.4±13.9	+2.3±12.6	NS	+2.2±14.9	NS
LOCF	+2.3±14.2	+2.9±12.7	NS	+1.6±14.4	NS
LDL cholesterol (%)					
RM	+6.1±22.2	+4.8±17.6	NS	+8.4±30.2	NS
LOCF	+7.0±22.4	+6.6±21.4	NS	+7.2±28.4	NS
Peak size of LDL particles (Å)					
RM	−0.5±1.4	−0.6±1.4	NS	−0.1±1.5	0.008
LOCF	−0.9±3.9	−1.0±4.1	NS	+0.3±3.8	<0.001
Proportion of small LDL (%)					
RM	+5.6±18.3	+3.9±13.7	NS	+0.4±15.8	0.007
LOCF	+3.2±18.8	+2.2±15.1	NS	−1.5±16.1	0.002
HDL cholesterol (%)					
RM	+12.2±15.5	+15.6±15.3	0.017	+23.4±21.8	<0.001
LOCF	+11.0±15.8	+14.2±17.6	0.025	+19.1±20.9	<0.001
Total cholesterol:HDL cholesterol ratio					
RM	−0.50±0.91	−0.57±0.81	NS	−0.84±0.93	<0.001
LOCF	−0.40±0.90	−0.47±0.82	NS	−0.72±0.93	<0.001
LDL cholesterol:HDL cholesterol ratio					
RM	−0.19±0.69	−0.31±0.62	NS	−0.41±0.76	<0.001
LOCF	−0.14±0.68	−0.23±0.65	NS	−0.35±0.76	<0.001
Apolipoprotein B:apolipoprotein A-I ratio†					
RM	0±0.13	−0.02±0.13	NS	−0.03±0.12	0.040
LOCF	0±0.12	−0.02±0.14	NS	−0.03±0.13	0.023
Fasting glucose (mmol/liter)					
RM	−0.02±0.60	+0.01±0.60	NS	−0.09±0.61	NS
LOCF	−0.05±0.62	−0.01±0.62	NS	−0.08±0.58	NS

had a weight loss equal to or greater than 5 percent was 19.5 percent in the placebo group and 58.4 percent in the group receiving 20 mg of rimonabant (P<0.001), whereas the proportion of those who had a weight loss equal to or greater than 10 percent was 7.2 percent in the placebo group and 32.6 percent in the group receiving 20 mg of rimonabant (P<0.001). Weight loss occurred during the first 9 months of the study period, after which body weight stabilized until the end of the 12th month

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 2. (Continued.)

End Point	Placebo Group	5-mg Rimonabant Group		20-mg Rimonabant Group	
			P Value		P Value
Fasting insulin (μU/ml)					
RM	+0.7±17.5	+0.6±10.0	NS	−1.3±7.9	0.011
LOCF	+0.9±15.9	+0.4±10.3	NS	−1.7±12.4	0.016
Adiponectin (μg/ml)‡					
RM	+0.8±1.8	+1.1±1.9	0.049	+2.7±2.5	<0.001
LOCF	+0.7±1.9	+1.0±2.0	NS	+2.2±2.5	<0.001
Leptin (ng/ml)					
RM	−0.3±5.8	−2.4±7.0	0.002	−4.8±7.7	<0.001
LOCF	−0.3±6.0	−2.3±7.9	<0.001	−4.1±7.4	<0.001
C-reactive protein (mg/liter)§					
LOCF	−0.4	−0.2	NS	−0.9	0.020
Safety end point					
Heart rate (bpm)¶	+0.7±8.3	+0.2±7.5	ND	+0.9±7.2	ND
Blood pressure (mm Hg)					
Systolic					
RM	−0.7±9.1	−0.4±11.3	NS	−3.6±10.9	0.015
LOCF	−0.3±10.1	+0.4±11.8	NS	−2.1±12.3	0.048
Diastolic					
RM	−0.8±7.3	−0.5±7.9	NS	−2.9±7.6	0.002
LOCF	−0.2±7.4	+0.1±8.3	NS	−1.7±8.5	0.011
QTc (msec)¶	−1.8±15.3	−3.7±16.9	ND	−4.6±15.7	ND
Depression¶‖	+0.2±2.7	−0.2±2.8	ND	+0.1±3.1	ND
Anxiety¶‖	+0.1±2.7	−0.1±3.5	ND	+0.3±3.0	ND

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, bpm beats per minute, NS not significant, and ND not determined. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6.

† The analysis was performed on a subgroup of patients (231, 224, and 237 patients in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

‡ The analysis was performed on a subgroup of patients (231, 222, and 238 patients in the placebo group, the group receiving 5 mg of rimonabant, and the group receiving 20 mg of rimonabant, respectively).

§ Values for the change from baseline were not normally distributed and are presented as medians, with statistical significance assessed nonparametrically with the use of an analysis of variance on ranked values.

¶ No statistical test was performed.

‖ The disorder was measured according to the hospital anxiety and depression scales.[14,16]

without evidence of regain (Fig. 1A). Changes in waist circumference showed a similar dose response (Table 2) and temporal pattern (Fig. 1B).

The caloric restriction during the four-week run-in period produced reductions of 5.3±37.9 percent in triglycerides, 4.9±17.2 percent in LDL cholesterol, and 3.6±11.9 percent in HDL cholesterol, which resulted in a 0.11±0.76 decrease in the total cholesterol:HDL cholesterol ratio (Table 1). During treatment, triglycerides remained stable in both the placebo group and the group receiving 5 mg of rimonabant but fell an additional 15.8±38.0 percent in the group receiving 20 mg of rimonabant (P<0.001) (Table 2 and Fig. 1C).

HDL cholesterol increased in a dose-dependent fashion, achieving an increase of 15.6±15.3 percent from baseline in the group receiving 5 mg of rimonabant (P=0.017) and of 23.4±21.8 percent in the group receiving 20 mg of rimonabant (P<0.001) (Table 2 and Fig. 1D). Although there was no change in levels of LDL cholesterol, the distribution of LDL particles shifted toward larger size in the group receiving 20 mg of rimonabant, as compared with placebo, with a difference of 1.1 Å in the peak

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

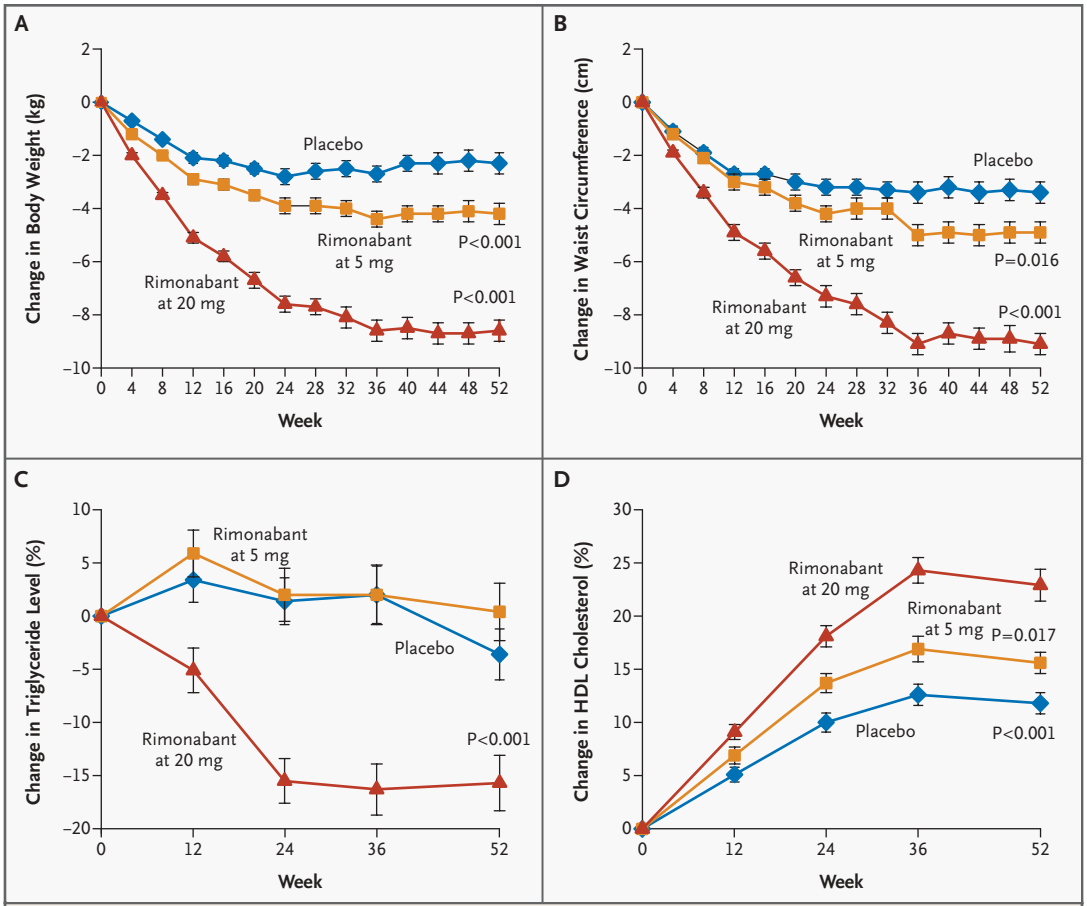


Figure 1. Effect of Placebo or Rimonabant for 52 Weeks on Body Weight, Waist Circumference, Plasma Triglyceride Levels, and High-Density Lipoprotein (HDL) Cholesterol Levels.

Body weight and waist circumference were measured at randomization (week 0) and every four weeks thereafter until week 52, and plasma HDL cholesterol and triglyceride levels were measured at randomization (week 0) and every three months thereafter until week 52. Values are shown as means ±SE for all patients for whom measurements were taken at each visit (lines); P values were obtained after the repeated-measures analysis. P values correspond to the mean difference between the rimonabant groups and the placebo group.

size of LDL particles (P=0.008) and a 4.6 percent lower proportion of small LDL particles (P=0.007) (Table 2). Changes in levels of HDL cholesterol translated into a dose-dependent reduction in the total cholesterol:HDL cholesterol ratio of −15.2 percent with 20 mg of rimonabant, which was greater than with placebo (P<0.001) (Table 2). Levels of fasting plasma insulin, the one-hour and two-hour plasma glucose and insulin levels, and the insulin and glucose AUCs during the 75-g oral glucose-tolerance test decreased significantly in the group receiving 20 mg of rimonabant (Fig. 2A and 2B; P=0.011 to <0.001).

At baseline, 54 percent of the patients who underwent randomization met the NCEP-ATPIII criteria for the metabolic syndrome (Table 1). The prevalence of the metabolic syndrome fell to 25.8 percent, 40.0 percent, and 41.0 percent in the groups receiving 20 mg of rimonabant, 5 mg of rimonabant, and placebo, respectively; the reduction in the group receiving 20 mg of rimonabant was significantly greater (P<0.001) than in the placebo group and was attributed mainly to the reduction in waist circumference and the increase in HDL cholesterol levels.

Plasma adiponectin levels increased with rimonabant treatment (at a dose of 20 mg) by 57.7 percent — an increase significantly greater than that observed in the placebo group (Fig. 2C). The increase correlated with weight loss in each group

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

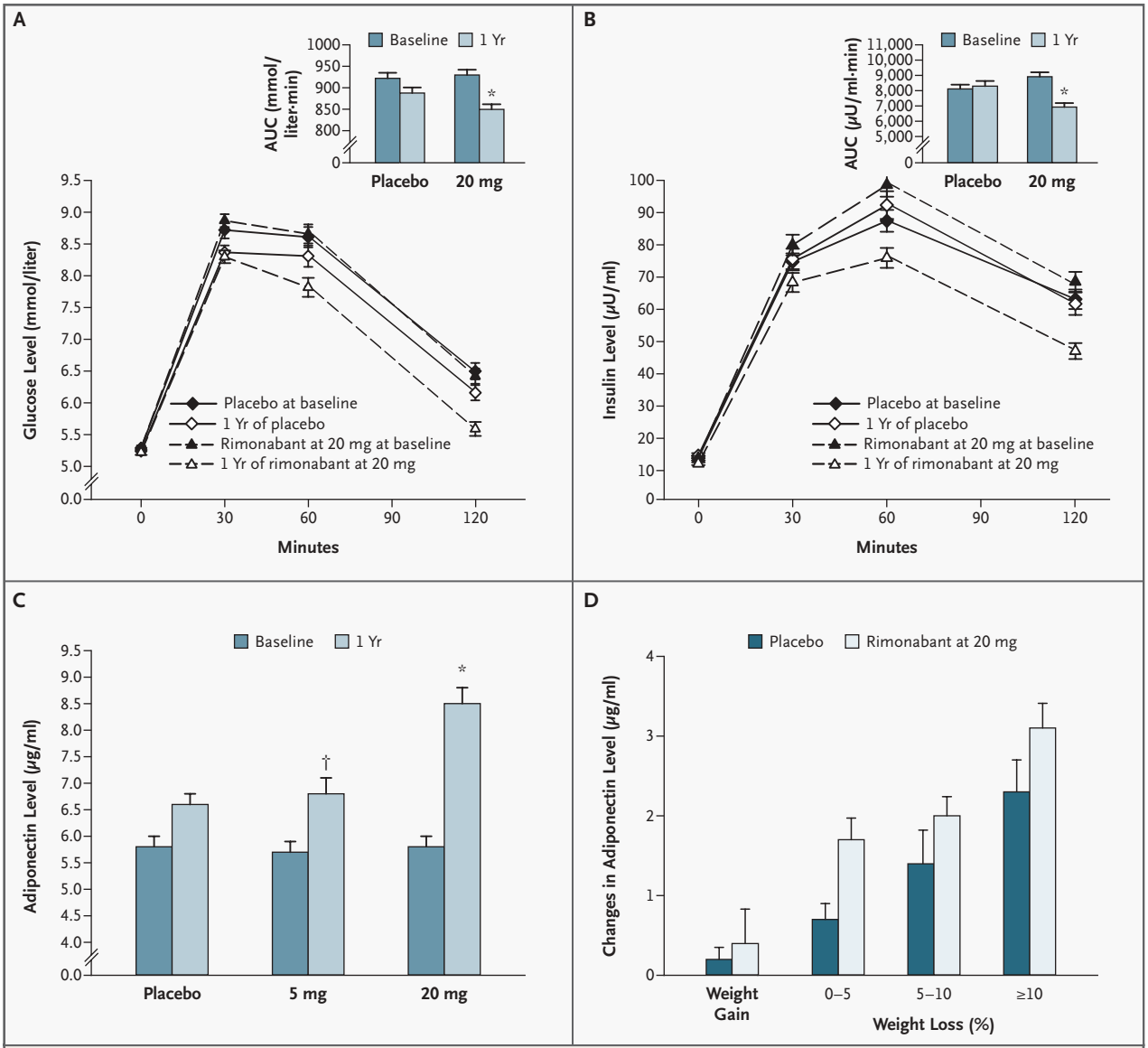


Figure 2. Effect of Placebo or 20 mg of Rimonabant for 52 Weeks on the Plasma Glucose and Insulin Responses to Oral Glucose Challenge (Panels A and B), and the Plasma Adiponectin Level (Panels C and D).

Values for plasma glucose and insulin were measured before the 75-g oral glucose challenge and 30, 60, and 120 minutes afterward, and values are shown for patients for whom measurements were available for each time point (Panels A and B). The integrated areas under the curves (AUCs) are shown in the insets with the P values obtained with the use of the repeated-measures analysis. Panel C shows the effect on plasma adiponectin levels, and Panel D shows the changes in adiponectin levels according to changes in body weight. P values correspond to the mean differences between the rimonabant groups and the placebo group. The asterisk denotes P<0.001, and the dagger P=0.049. To convert values for glucose to milligrams per deciliter, divide by 0.05551; to convert values for insulin to picomoles per liter, multiply by 6.

(r=−0.27, r=−0.30, and r=−0.26 in the placebo group, the 5-mg rimonabant group, and the 20-mg rimonabant group, respectively; P<0.001). However, 57 percent of the increase in adiponectin levels observed in the group receiving 20 mg of rimonabant could not be attributed to weight loss (Fig. 2D). Changes in adiponectin levels produced by rimonabant at a dose of 20 mg also positively correlated with changes in levels of HDL cholesterol (r=0.27, P<0.001) and apolipoprotein A-I (r=0.38, P<0.001).

Plasma leptin levels decreased significantly in the groups receiving 5 mg of rimonabant (P=0.002)

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 3. Adverse Events.

Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Adverse events — %*			
Nasopharyngitis	21.6	26.4	19.4
Headache	15.8	15.4	15.3
Nausea	3.2	7.2	12.7
Dizziness	6.7	8.4	10.4
Influenza	5.3	6.1	9.5
Upper respiratory tract infection	9.9	8.7	8.7
Anxiety	3.8	2.9	8.7
Back pain	10.2	9.6	7.2
Diarrhea	4.1	6.4	7.2
Gastroenteritis	6.4	4.3	6.6
Insomnia	2.6	4.1	6.4
Arthralgia	9.6	7.0	5.5
Serious adverse events — no. (%)†			
Infections and infestations	1 (0.3)	1 (0.3)	2 (0.6)
Surgical and medical procedures	1 (0.3)	0	0
Immune system disorders	2 (0.6)	0	0
Psychiatric disorders	1 (0.3)	1 (0.3)	1 (0.3)
Nervous system disorders	2 (0.6)	0	2 (0.6)
Eye disorders	0	1 (0.3)	0
Cardiac disorders	0	2 (0.6)	1 (0.3)
Vascular disorders	1 (0.3)	0	0
Gastrointestinal disorders	1 (0.3)	3 (0.9)	1 (0.3)
Hepatobiliary disorders	0	2 (0.6)	0
Musculoskeletal and connective-tissue disorders	1 (0.3)	4 (1.2)	2 (0.6)
Renal and urinary disorders	0	0	1 (0.3)
Reproductive system and breast disorders	0	2 (0.6)	1 (0.3)
Investigations	0	0	1 (0.3)
Injury, poisoning, and procedural complications	0	0	1 (0.3)
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	0	3 (0.9)	2 (0.6)

and 20 mg of rimonabant (P<0.001) in a dose-dependent fashion (Table 2). Plasma C-reactive protein levels decreased by 0.9 mg per liter in the group receiving 20 mg of rimonabant (P=0.020) (Table 2).

The proportions of patients who had treatment-related adverse events or serious adverse events were slightly higher in the group receiving 5 mg of rimonabant and the group receiving 20 mg of rimonabant than in the placebo group (treatment-related adverse events: 82.3 percent, 86.7 percent, and 81.6 percent, respectively; and serious adverse events: 5.2 percent, 4.0 percent, and 2.3 percent, respectively). There were no deaths in any of the three groups. The treatment-related adverse events reported in 5 percent or more of the patients in either rimonabant group but more commonly among those receiving 20 mg of rimonabant were (in order of decreasing frequency) nausea, dizziness, influenza, anxiety, diarrhea, and insomnia; these occurred early in the treatment period (Table 3). Overall discontinuation rates were similar in the three groups, but more patients discontinued treatment because of adverse effects in the group receiving 20 mg of rimonabant (Table 1) than in the other groups. The most frequent adverse events resulting in discon-

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Table 3. (Continued.)

Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Discontinuation — no. (%)‡			
Patients who discontinued participation	24 (7.0)	29 (8.4)	52 (15.0)
Reason for discontinuation			
Psychiatric disorders			
Depression	2 (0.6)	6 (1.7)	10 (2.9)
Anxiety	2 (0.6)	1 (0.3)	6 (1.7)
Major depression	0	2 (0.6)	2 (0.6)
Irritability	2 (0.6)	1 (0.3)	2 (0.6)
Aggression	0	1 (0.3)	2 (0.6)
Depressed mood	0	0	2 (0.6)
Sleep disorder	0	0	2 (0.6)
Insomnia	2 (0.6)	1 (0.3)	0
Nervous system disorders			
Dizziness	0	2 (0.6)	3 (0.9)
Amnesia	0	0	2 (0.6)
Headache	3 (0.9)	1 (0.3)	0
General disorders			
Fatigue	3 (0.9)	0	2 (0.6)
Gastrointestinal disorders			
Nausea	0	2 (0.6)	4 (1.2)
Dyspepsia	0	1 (0.3)	2 (0.6)
Upper abdominal pain	0	0	2 (0.6)
Vascular disorders			
Hypertension	1 (0.3)	2 (0.6)	1 (0.3)
Infections and infestations			
Pneumonia	2 (0.6)	0	0

* Adverse events are included if they occurred in at least 5 percent of either rimonabant group. They are listed according to preferred term.
† Serious adverse events are listed according to system organ class.
‡ Treatment-related adverse events are included if they occurred in at least 0.5 percent of any treatment group and resulted in a request to discontinue participation in the study. Events are listed according to system organ class and then preferred term for the event. Patients may have had more than one type of adverse event that led to discontinuation.

tinuation in the groups receiving rimonabant at 5 mg and 20 mg, as compared with placebo, included depression (1.7 percent and 2.9 percent, respectively, vs. 0.6 percent); anxiety (0.3 percent and 1.7 percent vs. 0.6 percent); and nausea (0.6 percent and 1.2 percent vs. 0 percent).

Values for laboratory safety measures linked to obesity (i.e., levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and uric acid) decreased with rimonabant at a dose of 20 mg (data not shown). Other values for safety measures included heart rate, systolic and diastolic blood pressure, QTc, and scores for anxiety and depression according to the hospital anxiety and depression scales (Table 1), and all except for blood pressure were similar in the three groups during the study period. Decreases in systolic and diastolic blood pressure with 20 mg of rimonabant were statistically significant (Table 2) and were greater among patients with hypertension at baseline (blood pressure, ≥140/90 mm Hg). For the 20-mg rimonabant versus placebo groups, the respective decreases in patients with hypertension were as follows: systolic pressure, 13.1±11.5

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

vs. 7.2±10.7 mm Hg, P=0.038; and diastolic pressure, 6.3±6.0 vs. 2.4±9.7 mm Hg, P=0.022. Finally, there were no interactions between treatment assignment and sex (data not shown).

DISCUSSION

The NCEP-ATPIII report and the recently published National Heart, Lung, and Blood Institute and American Heart Association consensus report highlighted abdominal obesity as assessed by waist circumference as an important cardiovascular risk marker and the primary target for the treatment of the metabolic syndrome.[15,19] Few tools exist to treat collectively the underlying pathophysiology in high-risk, abdominally obese patients, and most published obesity studies primarily enrolled patients who were at relatively low cardiovascular risk (i.e., obese women not selected for the presence of cardiovascular risk factors).[20] In the recent RIO-Europe study in obese patients, CB_1-receptor blockade with rimonabant was found to reduce body weight and waist circumference, improve plasma glucose–insulin homeostasis, and produce a substantial increase in plasma HDL cholesterol levels — a change that was greater than what could be expected from weight loss alone.[14] These findings suggested a weight-loss–independent effect of rimonabant on metabolic risk that may be mediated by the effect of rimonabant on adiponectin secretion by fat cells, as reported in studies in animals.[13]

Our study explored further the effect of rimonabant in a high-risk population of patients with dyslipidemia who are overweight or obese, with a focus on metabolic risk markers such as the size of LDL particles and levels of C-reactive protein and adiponectin. As compared with placebo, rimonabant at a dose of 20 mg per day induced significant weight loss and reduction in waist circumference, suggesting a substantial mobilization of abdominal fat, which, by itself, would predict an improved cardiovascular risk profile.[21] Additional effects of rimonabant at this dose, as compared with placebo, included significant improvements in plasma triglycerides, plasma HDL cholesterol, and the total cholesterol:HDL cholesterol ratio, as well as changes in LDL particle size, adiponectin levels, glucose tolerance, fasting and post-challenge insulin levels (markers for the risk of diabetes), and plasma C-reactive protein levels and in the proportion of patients meeting the NCEP-ATPIII criteria for the metabolic syndrome.

Rimonabant had no effect on LDL cholesterol levels. Patients with abdominal obesity and the metabolic syndrome generally do not have elevated levels of LDL cholesterol[22] but, rather, express the high triglyceride–low HDL cholesterol–small, dense LDL dyslipidemia associated with insulin resistance phenotype.[23] Although the LDL cholesterol level itself powerfully predicts cardiovascular risk,[24] the metabolic risk profile of abdominal obesity[23,25] further increases the risk of coronary heart disease for any level of LDL cholesterol.[26] In the RIO-Lipids study, the proportions of small and large LDL particles were altered with rimonabant, as compared with placebo, in the absence of any change in LDL cholesterol levels.

Although patients who meet the NCEP-ATPIII criteria for the metabolic syndrome have a distinct cardiovascular disease risk-factor profile, the clinical relevance of making the metabolic syndrome a treatable target beyond classic risk factors has been debated.[27] Therefore, the clinical relevance of reducing the proportion of patients meeting those NCEP-ATPIII criteria for the metabolic syndrome by the use of rimonabant can be questioned if it is not accompanied by favorable changes in markers for insulin resistance and abdominal obesity such as glucose tolerance and levels of insulin, adiponectin, and C-reactive protein, all of which, when abnormal, are linked to visceral obesity and the metabolic syndrome.[28,29] The results of the RIO-Lipids study with regard to C-reactive protein are thus consistent with the reported beneficial effect of weight loss on inflammation.[30,31] Whether the reduction in C-reactive protein levels will be additive to or synergistic with the reduction in C-reactive protein levels and the cardiovascular protection ascribed to statins and fibric acids[32,33] remains to be explored. Although regarded as the least prominent component of the metabolic syndrome,[34] hypertension is more prevalent among abdominally obese patients with insulin resistance, and the condition usually responds to weight loss.[35] Rimonabant at a dose of 20 mg reduced blood pressure overall, especially among patients with hypertension.

Finally, the results of the RIO-Lipids study provide evidence for a weight-loss–independent effect of rimonabant on adiponectin levels. This finding may be of clinical importance, since a high adiponectin level has been reported to be predictive of a reduced risk of diabetes and cardiovascular events.[36,37] Abdominal obesity is accompanied by reduced adiponectin levels, and such hypoadipo-

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

nectinemia is partly responsible for the low HDL cholesterol levels in abdominal obesity.[38] Since the changes in adiponectin levels observed in the present study correlated with changes in HDL cholesterol and apolipoprotein A-I, the stimulation of adiponectin production with CB_1-receptor blockade could explain the consistent and weight-loss–independent effect of rimonabant on HDL cholesterol levels in the RIO-Europe and RIO-Lipids studies.

In conclusion, although pharmacotherapy alone will not eradicate the epidemic of obesity, this study provides evidence that CB_1-receptor blockade may constitute a new, clinically relevant pharmacologic approach to improve the unfavorable cardiovascular risk profile in high-risk patients with dyslipidemia who are overweight or obese. The adverse-event profile of rimonabant observed in the RIO-Lipids study was found to be concordant with the results of the RIO-Europe study. Finally, the weight-loss–independent effect of rimonabant on plasma adiponectin levels is consistent with the reported in vitro effect of this CB_1-receptor blocker on adiponectin production by adipose cells.

Supported by Sanofi Aventis.

Dr. Després reports having received consulting or lecture fees from Abbott Laboratories, AstraZeneca, Fournier Pharma, GlaxoSmithKline, Merck, Pfizer, Pharmacia, and Sanofi Aventis and grant support from Fournier Pharma, GlaxoSmithKline, Merck, Pfizer, and Sanofi Aventis. Dr. Golay reports having received consulting or lecture fees from Hoffmann–La Roche, Abbott Laboratories, Merck, Pfizer, Servier, and Sanofi Aventis. Dr. Sjöström reports having received consulting or lecture fees from Biovitrum, GlaxoSmithKline, Johnson & Johnson, Merck, Roche, and Sanofi Aventis.

We are indebted to the members of the data safety monitoring board: Drs. Michael Weintraub, Jean-Louis Imbs, Alain Leizorovicz, Elliot Danforth, and David P.L. Sachs; and to the staff of the 67 clinical sites in eight countries (Australia, Canada, Finland, Italy, Spain, Sweden, Switzerland, and the United States) for their dedicated contribution to the study.

APPENDIX

The following investigators and coinvestigators participated in the study: D. Carey, N. Wood, G. Wittert, D. Jesudason, P. Phillips, M.T. Kuruvila, A. Sverdlov, H. Sia, J. Proietto, K. Bate, P. Colman, L. Rando, M. Hooper, C. Ting, N. Kormas, T. Markovic, K. Steinbeck, I. Kormas, N. Caterson, S. Li, J. Hui, V. Wong, J.-P. Després, A. Tremblay, N. Alméras, P. Poirier, R. Aronson, M.E. Alexander, L.G. Goluboff, Y. Twum-Barima, P. Whitsitt, R. Verdonk, C. Li, J.-P. Ouellet, P. Marchand, M. Bezeau, R. Girard, F. Ross, R. Goldenberg, R. Schlosser, R. Aronson, M.-C. Audet, D. Bélanger, M. Boutin, A. Martel, R. Boucher, P.-P. Côté, G. Tellier, F. Cousineau, Y. Pesant, P. Chevalier, G. Laurin, G. Girard, A. Crépeau, L. Frenette, R. Bouchard, C. St.-Pierre, F. Turcotte, M. Loyer, M. Drapeau, P. Pelletier, A. Dugas, A. Rissanen, J. Puhakka, K. Pietilainen, P. Broas, S. Keinanen-Kiukaanniemi, M. Laakso, R. Pasquali, B. Ambrosi, L. Frittitta, C.M. Rotella, R. Vettor, X. Formiguera, A. Almenara, R. Gomis, M.J. Coves, J. Vidal, B. Moreno, J. Rivera, A. Jimenez, A. Zugasti, M.D. Rodriguez, J. Salas, M.J. Jimenez, L. Sjöström, A.M. Langkilde, K. Vikman-Adolfsson, C. Ehrnborg, U. Adamson, L. Adamson, A. von Dobeln, T. Kjellstrom, P. Katzman, R. Rosin, I. Lager, L. Eden, A. Pagnamenta, G. Noseda, C. Fragiacomo, J. Zerega, M. Ghielmetti, T. Reynaldos, A. Golay, V. Makoundou, C. Ries, G. Gastaldi, V. Giusti, M.A. Adamczyk, M.R. Modiano, C.L. Hannah, R.B. Salazar, R. Armbruster, F.E. Dunlap, D. Brune, E. Rufus, A.J. Heritch, J. Cavanaugh, A. Delpilar, M.A. Ziboh, S. Chipkin, B.L. Haag, M.P. Roy, R.J. Cooper, E. Cohen, S. Klugh, O.M. Quijano, V. Reddy, L. Metchick, B. Egan, W.H. Bestermann, K. Nashar, A. Jesri, D. Fiske, J.M. Houri, T. Evans, D.B. George, S.M. George, S. Polyhronopoulos, B.F. Scott, R.V. Steeves, J.L. Kantlehner, P.A. Warner, T.C. Harris, W.K. Kleinsteuber, G.T. Gerhard, S.J. Redmond, T. Passmore, E. Glover, C.R. Sullivan, P.N. Glover, C.L. Cerullo, J.H. Berry, S.C. Yerneni, R.M. Griffin, P.D. Nicholas, M.A. Borofsky, J.S. Weisberg, W. Santoro, C.H. Schmidley, J.T. Van Den Bosch, J.T. Lumley, D.F. Steffy, P.J. Baney, C.A. Wagner, E. Krishnan, L. Gringeri, A.F. Marchesani, C.W. Clark, D. Torelli, G.K. Phillips, L. Denton, S.M. Kneiss, L.G. Kelner, R. Rosenberg, S.B. Jones, D.B. Vine, A. Kivitz, S.P. Kafka, F.T. Murphy, V.M. Sommer, L.A. Krug, D.L. Rentz, S.K. Ritchey, M.J. Zumer, M. Dubeck, A. Maldonado, C. Cunningham, M.J. Koren, S. Greco, J.A. Jacqmein, D. Robinson, J.C. Hackenberg, D.M. Bartilluci, M.N. Lunde, M.J. Zarama-Medina, M.G. Somermeyer, E.A. Holum, S.L. McElroy, P.E. Keck, E. Nelson, R. Kotwal, S. Malhotra, L. Arnold, B. Martens, R. Kowatch, W.J. Mroczek, B.L. Berliner, J. Klein, A.R. George, W.P. Jennings, R. Nett, C.F. Serna, T.R. Weiss, M. Nides, D. Medway, H. Eisenbach, E. Marshall, S.E. Prohaska, R.E. Pruitt, D. Jacobus, R.W. Herring, J.B. Rosen, I.G. Carrasquilla, H.M. Silberman, C.K. Mitch-Gomez, S. Yahia, C.F. Yanes, S. Duncan-Garcia, S. Rosenblatt, J.M. Wilson, E.R. Lee, M.A. Flanagan, L. Rudolph, E.M. Lewiecki, E.W. Best, J. Chavez, I. Garcia, M. Gurule, L. Ierides, R.L. Romanik, G. Shockey, A.M. Germaine, K.L. Valderhaug, J.A. Brown, M. Smith, R. Laufer, L.D. Smith, R. Chan, C.R. Ellsworth, K.R. Becker, R.L. Goldman, W.B. Smith, A.B. Alper, G.M. Johnson, R.L. Gibson, R.K. Mautner, S.G. Swanson, J.J. Maly, P. Gillapsie, M.M. Snow, P. Railsback, J. Oden, R. Tanous, T.P. Hutchens, R.J. Bury, S.S. Bradley, J. Akhter, S.J. Scherr, K.R. Happel, M.J. Tonkon, E.R. Ross, N.C. Morcos, D.M. See, P. Rand, P.D. Toth, D.C. Weiser, J. Zavoral, J.M. Beard, C.J. Baumgartner, F.J. Zieve, J.R. Levy, S.K. Frederickson, D.I. Panebianco, K.A. Tidsel, B. Lindgren, and H. Zacur.

REFERENCES

1. Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. Cell 2004;116:337-50.
2. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov 2004;3:771-84.
3. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003;112:423-31.
4. Horvath TL. Endocannabinoids and the regulation of body fat: the smoke is clearing. J Clin Invest 2003;112:323-6.
5. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946-9.
6. Hanus L, Abu-Lafi S, Fride E, et al. 2-Arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci U S A 2001;98:3662-5.
7. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54:161-202.
8. Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001;410:822-5.
9. Kirkham TC, Williams CM, Fezza F, Di Marzo V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimula-

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

tion of eating by 2-arachidonoyl glycerol. Br J Pharmacol 2002;136:550-7.
10. Pagotto U, Pasquali R. Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors. Lancet 2005; 365:1363-4.
11. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29-33.
12. Jbilo O, Ravinet-Trillou C, Arnone M, et al. The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. FASEB J 2005;19:1567-9.
13. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003;63:908-14.
14. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365:1389-97.
15. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
17. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. Circulation 2001;104:2295-9.
18. Laboratory test handbook. 4th ed. Hudson (Cleveland): Lexi-Comp, 1996.
19. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.
20. Després JP. Drug treatment for obesity: we need more studies in men at higher risk of coronary events. BMJ 2001;322:1379-80.
21. Ross R, Dagnone D, Jones PJ, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. Ann Intern Med 2000;133:92-103.
22. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497-511.
23. Tchernof A, Lamarche B, Prud'homme D, et al. The dense LDL phenotype: association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. Diabetes Care 1996;19:629-37.
24. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282:2340-6.
25. Rainwater DL. Lipoprotein correlates of LDL particle size. Atherosclerosis 2000;148: 151-8.
26. Assmann G. Pro and con: high-density lipoprotein, triglycerides, and other lipid subfractions are the future of lipid management. Am J Cardiol 2001;87:2B-7B.
27. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28:2289-304.
28. Lemieux I, Pascot A, Prud'homme D, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol 2001;21:961-7.
29. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation 2004;109: 2818-25.
30. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002;105:564-9.
31. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Arterioscler Thromb Vasc Biol 2001;21:968-70.
32. Staels B, Koenig W, Habib A, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. Nature 1998;393:790-3.
33. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286: 64-70.
34. Meigs JB, D'Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. Diabetes 1997;46:1594-600.
35. Kanai H, Tokunaga K, Fujioka S, Yamashita S, Kameda-Takemura KK, Matsuzawa Y. Decrease in intra-abdominal visceral fat may reduce blood pressure in obese hypertensive women. Hypertension 1996; 27:125-9.
36. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7.
37. Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8. [Erratum, Lancet 2002;361:1060.]
38. Côté M, Mauriège P, Bergeron J, et al. Adiponectinemia in visceral obesity: impact on glucose tolerance and plasma lipoprotein and lipid levels in men. J Clin Endocrinol Metab 2005;90:1434-9.

Copyright © 2005 Massachusetts Medical Society.

POWERPOINT SLIDES OF *JOURNAL* FIGURES AND TABLES

At the *Journal*'s Web site, subscribers can automatically create PowerPoint slides of *Journal* figures and tables. Click on a figure or table in the full-text version of any article at **www.nejm.org**, and then click on PowerPoint Slide for Teaching. A PowerPoint slide containing the image, with its title and reference citation, can then be downloaded and saved.

Downloaded from www.nejm.org by MS ELLEN INGERMAN on November 30, 2007 .
Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Exhibit C

NYPL RESEARCH LIBRARIES
3 3433 06746450 7

DELIVERY
DESK
SIBL

JAMA : the journal of the American Medical Association.
v. 295
no. 7
Feb 15, 2006

February 15, 2006

THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW (TITLE 17, U.S. CODE)

$BXBKCHY **********$AUTO**5-DIGIT 10163
$0000002951628JAMED14 02151227O6P0016 0016
NEW YORK PUBLIC LIBR SCIENCE I P134
LIB GRAND CENTRAL STATION 422
PO BOX 2233
NEW YORK NY 10163-2233

NYPL RESEARCH LIBRARIES
3 3433 06746450 7

February 15, 2006

DELIVERY
DESK
STRL

JAMA : the journal of the
American Medical
Association
v. 295,
no. 7
Feb. 15, 2006

$BXBKCHY **********AUTO**5-DIGIT 10163
000000295162JAME014 0215122706P0016 0016
NEW YORK PUBLIC LIBR SCIENCE I P134
LIB GRAND CENTRAL STATION 422
PO BOX 2233
NEW YORK NY 10163-2233

JAMA CONTACT INFORMATION

EDITORIAL OFFICE

JAMA, 515 N State St, Chicago, IL 60610, USA; phone: 312-464-2402; fax: 312-464-5824; e-mail: jamams@jama-archives.org.

Manuscript Submission: Manuscripts should be submitted online via the JAMA online manuscript submission and review system at http://manuscripts.jama.com (note: do not use www in the URL for manuscript submission).

Instructions for Authors: Published in the first issue of each January and July and available online at www.jama.com.

Letters to the Editor: Lisa Hardin; phone: 312-464-2405; e-mail: Lisa.Hardin@jama-archives.org.

Book and Media Reviews: Harriet Meyer, MD; phone: 312-464-2421; e-mail: Harriet.Meyer@jama-archives.org.

JAMA/ARCHIVES MEDIA RELATIONS

Jann Ingmire; phone: 312-464-JAMA (5262); e-mail: mediarelations@jama-archives.org.

JAMA ONLINE

JAMA is available online at www.jama.com.

PERMISSIONS

Information about obtaining permission to republish or adapt material published in *JAMA* is available from Rhonda Bailey Brown; phone: 312-464-2513; fax: 312-464-5843; e-mail: permissions@ama-assn.org.

JAMA/ARCHIVES REPRINTS

Author Reprints: Anna Goins; phone: 312-464-2477; fax: 312-464-5843; e-mail: Anna.Goins@ama-assn.org. Minimum order: 100 reprints.

Educational Reprints: Rhonda Bailey Brown; phone: 312-464-2513; fax: 312-464-5843; e-mail: Rhonda.Brown@ama-assn.org. Minimum order: 100 reprints.

Commercial Reprints: Phone: 312-464-0776; fax: 312-464-0708; e-mail: reprints@ama-assn.org. Minimum order: 500 reprints.

DOCUMENT DELIVERY

Copies of individual articles are available online at www.jama.com and from the following: Infotrieve, phone: 800-422-4633; fax: 310-208-5971; URL: www.infotrieve.com; e-mail: orders@infotrieve.com; Institute for Scientific Information (ISI), phone: 800-603-4367; fax: 856-787-1679; URL: www.isidoc.com; e-mail: service@isidoc.com.

INTERNATIONAL EDITIONS

JAMA is published in multiple international editions and languages. For more information, contact Millette Jackson-Bates; phone: 312-464-4868; fax: 312-464-5834; e-mail: Millette.Jackson@ama-assn.org.

JAMA (ISSN 0098-7484) is published weekly by the American Medical Association, except for 4 combined issues in months with 5 Wednesdays. Periodicals postage paid at Chicago and at additional mailing offices. GST registration number 12622 5556 RT. *JAMA* is registered in the US patent and trademark office. POSTMASTER, send all address changes to *JAMA*, c/o the AMA Unified Service Center, American Medical Association, 515 N State St, Chicago, IL 60610.

Copyright © 2006 by the American Medical Association

ADVERTISING

Information about advertising is available from the following sales representatives and online at www.jama.com.

Display Advertising: Susan J. Carollo, Maureen A. Reichert, Nancy E. Souza, 119 Cherry Hill Rd, Suite 330, Parsippany, NJ 07054; phone: 973-263-9191; e-mail: Susan.Carollo@ama-assn.org, Maureen.Reichert@ama-assn.org, Nancy.Souza@ama-assn.org.

Classified Advertising: Thalia Moss, 515 N State St, Chicago, IL 60610; phone: 800-262-2260; e-mail: classifieds@ama-assn.org.

ADVERTISING PRINCIPLES

Advertisements in this issue have been reviewed to comply with the principles governing advertising in *JAMA/Archives* Journals. A copy of these principles is available on request and online at www.jama.com. The appearance of advertising in *JAMA* is not a guarantee or endorsement of the product or the claims made for the product by the manufacturer.

ADDRESS CHANGES

Send all address changes to *JAMA*, c/o the AMA Unified Service Center, American Medical Association, 515 N State St, Chicago, IL 60610. Notification of address changes must be made at least 6 weeks in advance; include both old and new addresses and a recent mailing label if sending via mail.

SUBSCRIPTION RATES AND SERVICE

Subscription rates are shown in the table below. AMA members receive reduced rates. For service in the United States and the Americas, inquiries on pricing, address changes, missing issues, subscription billing, subscription renewal, and back issues, contact the AMA Unified Service Center, 24 hours a day, 7 days a week.

AMA Members: $20 per year in the United States (included in and not deductible from the annual AMA membership dues); phone: 800-262-3211; e-mail: msc@ama-assn.org.

Other Physicians and Nonphysician Customers, Including Subscription Agents: phone: 800-262-2350 or 312-670-7827; fax: 312-464-5831; e-mail: ama-subs@ama-assn.org.

Inquiries: Unified Service Center, American Medical Association, PO Box 10946, Chicago, IL 60610-0946. For subscribers with mailing addresses outside the United States and the Americas: Contact *JAMA & Archives* Journals, c/o EMD GmbH, Birkenstr.67, 10559 Berlin, Germany. Phone: +49 (30) 33099828; fax: +49 (30) 33099829; e-mail: ama@emd-germany.de.

	United States	Americas	United Kingdom	Rest of World
INDIVIDUAL				
Print and Online	$165	$220	£140	€210
INSTITUTION				
Print and Online	$450	$575	£335	€500

In Canada, US rate plus GST. Rates for residents and medical students available at pubs.ama-assn.org, or from the AMA Unified Service Center.

ORIGINAL CONTRIBUTION

Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients

RIO-North America: A Randomized Controlled Trial

F. Xavier Pi-Sunyer, MD
Louis J. Aronne, MD
Hassan M. Heshmati, MD
Jeanne Devin, MS
Julio Rosenstock, MD
for the RIO-North America Study Group

Context Rimonabant, a selective cannabinoid-1 receptor blocker, may reduce body weight and improve cardiometabolic risk factors in patients who are overweight or obese.

Objective To compare the efficacy and safety of rimonabant with placebo each in conjunction with diet and exercise for sustained changes in weight and cardiometabolic risk factors over 2 years

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of 3045 obese (body mass index ≥30) or overweight (body mass index >27 and treated or untreated hypertension or dyslipidemia) adult patients at 64 US and 8 Canadian clinical research centers from August 2001 to April 2004.

Intervention After a 4-week single-blind placebo plus diet (600 kcal/d deficit) run-in period, patients were randomized to receive placebo, 5 mg/d of rimonabant, or 20 mg/d of rimonabant for 1 year. Rimonabant-treated patients were rerandomized to receive placebo or continued to receive the same rimonabant dose while the placebo group continued to receive placebo during year 2.

Main Outcome Measures Body weight change over year 1 and prevention of weight regain during year 2. Additional efficacy measures included changes in waist circumference, plasma lipid levels, and other cardiometabolic risk factors.

Results At year 1, the completion rate was 309 (51%) patients in the placebo group, 620 (51%) patients in the 5 mg of rimonabant group, and 673 (55%) patients in the 20 mg of rimonabant group. Compared with the placebo group, the 20 mg of rimonabant group produced greater mean (SEM) reductions in weight (−6.3 [0.2] kg vs −1.6 [0.2] kg, $P<.001$), waist circumference (−6.1 [0.2] cm vs −2.5 [0.3] cm, $P<.001$), and level of triglycerides (percentage change, −5.3 [1.2] vs 7.9 [2.0]; $P<.001$) and a greater increase in level of high-density lipoprotein cholesterol (percentage change, 12.6 [0.5] vs 5.4 [0.7], $P<.001$). Patients who were switched from the 20 mg of rimonabant group to the placebo group during year 2 experienced weight regain while those who continued to receive 20 mg of rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors. Use of different imputation methods to account for the high rate of dropouts in all 3 groups yielded similar results. Rimonabant was generally well tolerated; the most common drug-related adverse event was nausea (11.2% for the 20 mg of rimonabant group vs 5.8% for the placebo group).

Conclusions In this multicenter trial, treatment with 20 mg/d of rimonabant plus diet for 2 years promoted modest but sustained reductions in weight and waist circumference and favorable changes in cardiometabolic risk factors. However, the trial was limited by a high drop-out rate and longer-term effects of the drug require further study

Clinical Trials Registration ClinicalTrials.gov Identifier: NCT00029861

JAMA. 2006;295:761-775 www.jama.com

ROUGHLY TWO THIRDS OF US adults meet the criteria for overweight or obesity,[1] which greatly increases the risk of developing diabetes mellitus and cardiovascular disease[2] and related mortality.[3] In addition to weight loss, obesity management should target reduction in the cardiometabolic risk factors of atherogenic dyslipidemia, excess abdominal obesity, and elevated glucose. Modest (approximately 5% to 10% of body weight) intentional nonpharmacological weight loss improves obesity-related cardiovascular and metabolic abnormalities[4] but diet and exercise interventions have limited long-term success. As a result, long-term weight management remains a challenge for patients and clinicians.

The endocannabinoid system regulates energy homeostasis through G protein–coupled cannabinoid-1 receptors[5,6] located in the central nervous system and in various peripheral tissues, including adipose tissue, muscle,

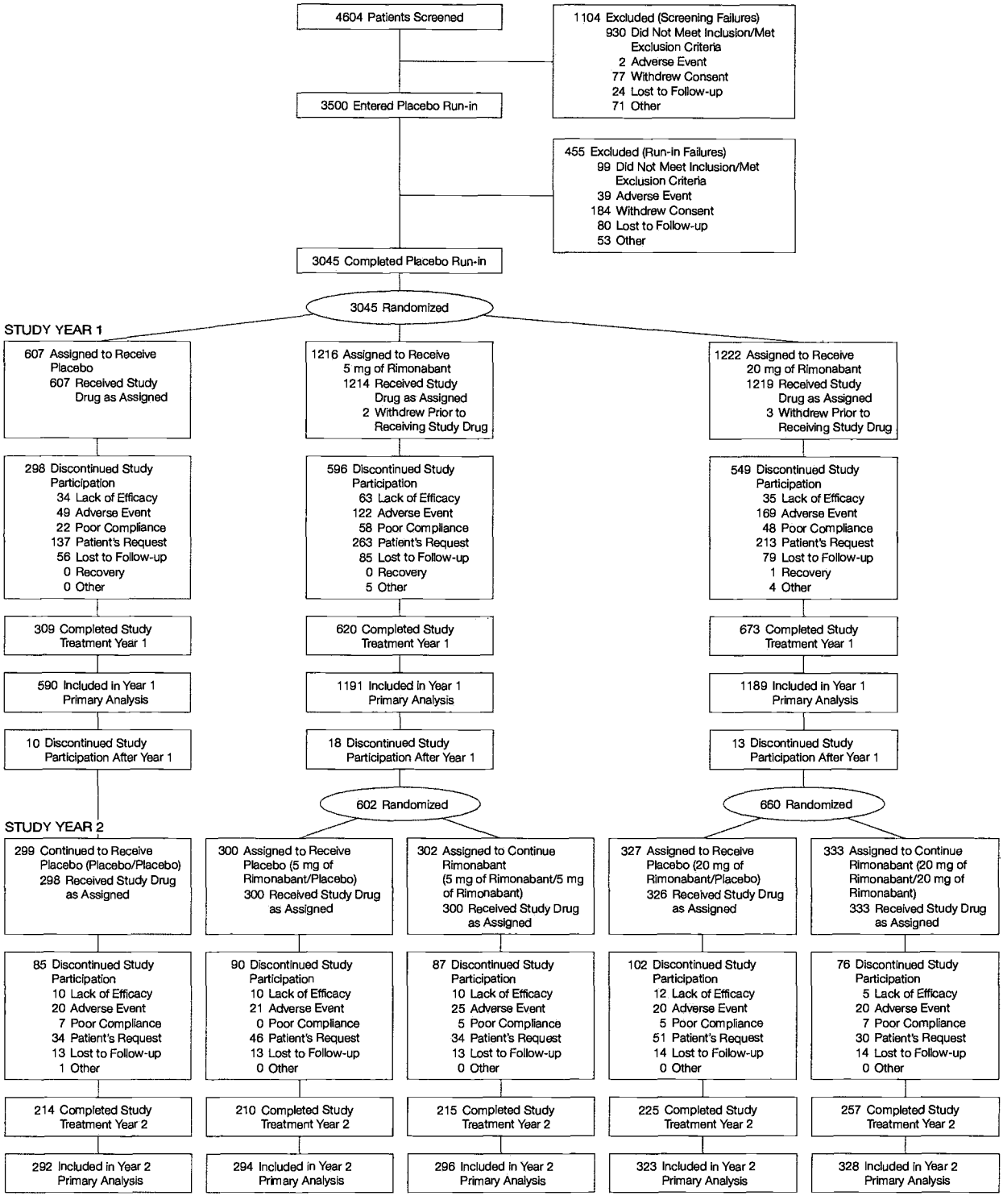
For editorial comment see p 826.

Author Affiliations are listed at the end of this article.
Corresponding Author: F. Xavier Pi-Sunyer, MD, Obesity Research Center, St Luke's-Roosevelt Hospital, 1111 Amsterdam Ave, WH1020, New York, NY 10025 (fxp1@columbia.edu).

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Figure 1. Flow Diagram of RIO-North America Trial



©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

the gastrointestinal tract, and the liver [7] While peripheral cannabinoid-1 receptor activation decreases adiponectin production in adipocytes,[8] central cannabinoid-1 receptor activation in preclinical studies stimulates eating, decreases muscle, and stimulates hepatic and adipose tissue lipogenic pathways in animal models of obesity.[9] In genetic and diet-induced obesity, rimonabant, a selective cannabinoid-1 receptor blocker, reduces overactivation of the central[8,10] and peripheral[11,12] endocannabinoid system[8,10,13] and prevents weight gain and associated metabolic disorders, thus revealing a novel strategy for the treatment of obesity and related cardiometabolic disorders.

Table 1. Patient Characteristics at Baseline According to First Randomized Treatment Assignment*

	Placebo (n = 607)	5 mg of Rimonabant (n = 1214)	*P* Value vs Placebo	20 mg of Rimonabant (n = 1219)	*P* Value vs Placebo
Race					
White	516 (85.0)	1010 (83.2)	.56	1027 (84.2)	.79
Black	67 (11.0)	140 (11.5)		132 (10.8)	
Sex					
Male	113 (18.6)	245 (20.2)	.43	230 (18.9)	.90
Female	494 (81.4)	969 (79.8)		989 (81.1)	
Age, y					
Overall, mean (SD)	44.8 (11.6)	44.4 (11.3)	.16	45.6 (11.8)	.47
18-44	277 (45.6)	624 (51.4)		560 (45.9)	
45-64	304 (50.1)	540 (44.5)		594 (48.7)	
≥65	26 (4.3)	50 (4.1)		65 (5.3)	
Body mass index					
Overall, mean (SD)	37.6 (6.4)	38.0 (6.7)	.16	37.2 (6.2)	.35
≤27	0	0		1 (<0.1)	
>27-<30	16 (2.6)	25 (2.1)		27 (2.2)	
≥30-<35	207 (34.1)	397 (32.7)		465 (38.1)	
≥35-<40	189 (31.1)	378 (31.1)		347 (28.5)	
≥40	195 (32.1)	414 (34.1)		379 (31.1)	
Weight, mean (SD), kg	105.0 (21.8)	105.5 (21.9)	.06	103.0 (20.3)	.65
Waist circumference, mean (SD), cm	106.0 (15.1)	106.5 (15.7)	.13	104.9 (15.0)	.48
Height, mean (SD), cm	167 (9)	166 (9)	.24	166 (9)	.55
Lipids, mean (SD), mg/dL					
HDL cholesterol	49 (12)	48 (12)	.58	49 (13)	.72
Triglycerides	133 (73)	139 (78)	.36	137 (80)	.18
Ratio of total cholesterol to HDL cholesterol, mean (SD)	4.18 (1.07)	4.26 (1.10)	.86	4.19 (1.13)	.12
Fasting glucose, mean (SD), mg/dL	92 (11)	92 (11)	.52	92 (11)	.89
Fasting glucose status					
Normal (<110 mg/dL)	576 (95.2)	1158 (95.8)	.68	1142 (94.0)	.53
Impaired (110-<126 mg/dL)	24 (4.0)	39 (3.2)		58 (4.8)	
Diabetic (≥126 mg/dL)	5 (0.8)	12 (1.0)		15 (1.2)	
Fasting insulin, mean (SD), μIU/mL	13.4 (10.0)	12.9 (11.0)	.30	12.9 (9.8)	.37
Insulin resistance derived from homeostasis model assessment, mean (SD)	3.1 (2.7)	3.0 (3.5)	.42	3.0 (2.7)	.53
Blood pressure, mean (SD), mm Hg					
Systolic	121.7 (12.4)	121.9 (12.7)	.96	121.7 (12.7)	.75
Diastolic	78.1 (7.8)	78.2 (8.1)	.27	77.7 (8.2)	.98
Disease/disorder					
Hypertension†	168 (27.7)	367 (30.2)	.26	390 (32.0)	.06
Dyslipidemia‡	388 (63.9)	767 (63.2)	.76	749 (61.5)	.31
The metabolic syndrome§	192 (31.8)	438 (36.3)	.06	419 (34.6)	.23
Current smoker	64 (10.5)	102 (8.4)	.09	118 (9.7)	.30

Abbreviation: HDL, high-density lipoprotein.
SI conversion factors: HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.
*Values are expressed as number (percentage) unless otherwise indicated. Continuous parameters were analyzed using analysis of variance and categorical parameters were analyzed using the χ^2 test.
†Defined as systolic blood pressure of 140 mm Hg or higher and/or supine diastolic blood pressure of 90 mm Hg or higher
‡Defined as low-density lipoprotein cholesterol level of 130 mg/dL or higher, HDL cholesterol level of less than 40 mg/dL, and/or triglycerides level of 150 mg/dL or higher
§Defined as abdominal obesity (waist circumference) of greater than 102 cm for men and of greater than 88 cm for women, triglycerides level of 150 mg/dL or higher; HDL cholesterol level of less than 40 mg/dL for men and less than 50 mg/dL for women, systolic blood pressure of 130 mm Hg or higher and diastolic blood pressure of 85 mm Hg or higher; and fasting glucose level higher than 110 mg/dL.

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Table 2. Placebo-Subtracted Changes From Baseline Body Weight and Cardiometabolic Risk Factors for Year 1*

	Last Observation Carried Forward	Baseline Imputed	Repeated Measures
Weight, kg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−1.3 (0.3)	−1.2 (0.3)	−1.8 (0.4)
95% CI	(−2.0 to −0.7)	(−1.8 to −0.6)	(−2.6 to −0.9)
P value	<.001	<.001	<.001
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−4.7 (0.3)	−4.2 (0.3)	−5.9 (0.4)
95% CI	(−5.4 to −4.1)	(−4.8 to −3.6)	(−6.8 to −5.0)
P value	<.001	<.001	<.001
HDL cholesterol, %			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	2.3 (0.9)	1.8 (0.7)	2.4 (1.0)
95% CI	(0.6 to 4.0)	(0.4 to 3.2)	(0.4 to 4.4)
P value	.01	.01	.02
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	7.2 (0.9)	6.2 (0.7)	8.6 (1.0)
95% CI	(5.6 to 8.9)	(4.8 to 7.7)	(6.6 to 10.6)
P value	<.001	<.001	<.001
Triglycerides, %			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−4.2 (2.3)	−4.1 (2.0)	−6.6 (2.8)
95% CI	(−8.8 to 0.3)	(−7.9 to −0.2)	(−12.0 to −1.2)
P value	.07	.04	.02
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−13.2 (2.3)	−11.4 (2.0)	−16.1 (2.7)
95% CI	(−17.7 to −8.7)	(−15.2 to −7.6)	(−21.5 to −10.8)
P value	<.001	<.001	<.001
Ratio of total cholesterol to HDL cholesterol			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.14 (0.04)	−0.10 (0.03)	−0.15 (0.04)
95% CI	(−0.21 to −0.07)	(−0.15 to −0.04)	(−0.24 to −0.07)
P value	<.001	<.001	<.001
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.28 (0.04)	−0.22 (0.03)	−0.32 (0.04)
95% CI	(−0.35 to −0.21)	(−0.28 to −0.16)	(−0.40 to −0.23)
P value	<.001	<.001	<.001
Waist circumference, cm			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.6 (0.3)	−0.6 (0.3)	−0.9 (0.4)
95% CI	(−1.3 to 0.1)	(−1.2 to 0.1)	(−1.8 to 0)
P value	.08	.08	.05
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−3.6 (0.3)	−3.2 (0.3)	−4.5 (0.4)
95% CI	(−4.3 to −2.9)	(−3.9 to −2.6)	(−5.4 to −3.7)
P value	<.001	<.001	<.001
Fasting glucose, mg/dL			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.38 (0.59)	−0.12 (0.49)	−0.31 (0.75)
95% CI	(−1.54 to 0.77)	(−1.09 to 0.84)	(−1.78 to 1.16)
P value	.52	.80	.68
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.65 (0.59)	−0.48 (0.49)	−0.69 (0.74)
95% CI	(−1.80 to 0.51)	(−1.44 to 0.49)	(−2.14 to 0.77)
P value	.27	.33	.36
Fasting insulin, μIU/mL			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−1.7 (0.7)	−1.3 (0.6)	−1.7 (0.8)
95% CI	(−3.0 to −0.4)	(−2.4 to −0.2)	(−3.2 to −0.2)
P value	.01	.02	.03
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−2.8 (0.7)	−2.2 (0.6)	−2.7 (0.8)
95% CI	(−4.1 to −1.5)	(−3.4 to −1.1)	(−4.2 to −1.2)
P value	<.001	<.001	<.001

(continued)

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Table 2. Placebo-Subtracted Changes From Baseline Body Weight and Cardiometabolic Risk Factors for Year 1 (cont)

	Last Observation Carried Forward	Baseline Imputed	Repeated Measures
Insulin resistance derived from homeostasis model assessment			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.6 (0.2)	−0.4 (0.2)	−0.6 (0.3)
95% CI	(−1.0 to −0.1)	(−0.8 to −0.1)	(−1.2 to −0.1)
P value	.01	.02	.02
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.8 (0.2)	−0.6 (0.2)	−0.8 (0.3)
95% CI	(−1.2 to −0.4)	(−1.0 to −0.3)	(−1.4 to −0.3)
P value	<.001	<.001	.001
Systolic blood pressure, mm Hg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.2 (0.6)	0.2 (0.5)	0.2 (0.8)
95% CI	(−0.9 to 1.4)	(−0.9 to 1.2)	(−1.3 to 1.7)
P value	.69	.72	.81
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.2 (0.6)	−0.3 (0.5)	−0.3 (0.8)
95% CI	(−1.4 to 1.0)	(−1.3 to 0.8)	(−1.8 to 1.2)
P value	.75	.62	.66
Diastolic blood pressure, mm Hg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.5 (0.4)	0.3 (0.4)	0.2 (0.5)
95% CI	(−0.3 to 1.3)	(−0.5 to 1.0)	(−0.8 to 1.2)
P value	.24	.47	.73
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.2 (0.4)	0 (0.4)	−0.2 (0.5)
95% CI	(−0.6 to 1.0)	(−0.8 to 0.7)	(−1.2 to 0.8)
P value	.66	.93	.65

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein cholesterol.
SI conversion factors: HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.
*Results shown according to method of imputation.

The RIO-North America trial evaluated the efficacy and safety of rimonabant in conjunction with a hypocaloric diet in promoting reductions in body weight and waist circumference, long-term weight maintenance, and amelioration of cardiometabolic risk factors in obese and higher-risk overweight patients

METHODS

Patients

Men and women aged 18 years or older were recruited at 64 US and 8 Canadian clinical research centers between September 2001 and April 2002 (FIGURE 1 and TABLE 1). Entry criteria included body mass index (calculated as weight in kilograms divided by the square of height in meters) of 30 or greater (obese) or body mass index of higher than 27 (overweight and treated or untreated dyslipidemia or hypertension). Patients were excluded if they had a body weight fluctuation of more than 5 kg in the previous 3 months, clinically significant cardiac, renal, hepatic, gastrointestinal tract, neuropsychiatric, or endocrine disorders; drug-treated or diagnosed type 1 or type 2 diabetes; use of medications that alter body weight or appetite; a history or current substance abuse; or changes in smoking habits or smoking cessation within the past 6 months. Women with childbearing potential were required to use medically approved contraception. Determination of race, a US Food and Drug Administration requirement, was by patient self-identification.

Study Design

RIO-North America was a 2-year, randomized, double-blind, placebo-controlled trial. The institutional review boards at each center reviewed and approved the study protocol and patients provided written informed consent before entry into the trial. Following a 1-week screening period, patients were instructed to follow a hypocaloric diet (approximately 600 kcal/d deficit) that was continued during a 4-week placebo, single-blind, run-in period and then throughout the double-blind treatment period. The diet prescription was adjusted to each patient's basal metabolic rate estimated by the Harris-Benedict equation[14] and self-reported physical activity at screening and at weeks 24, 52, and 76. Patients also were instructed to increase their level of physical activity throughout the study.

Patients who completed the run-in period were randomly allocated to 1 of 3 double-blind treatment groups for 1 year: placebo, 5 mg/d of rimonabant, or 20 mg/d of rimonabant. A predefined randomization schedule assigned patients using a block size of 5 and a randomization ratio of 1:2:2 to ensure sufficient numbers of rimonabant-treated patients for a rerandomization (1:1) for year 2. Rimonabant-treated patients were rerandomized to receive placebo or continued to receive the same rimonabant dose while the placebo

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Table 3. Placebo-Subtracted Changes From Baseline in Weight and Cardiometabolic Risk Factors for Year 2 for Patients Who Received the Same Treatment in Both Years*

	Last Observation Carried Forward	Baseline Imputed	Repeated Measures
Weight, kg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.8 (0.3)	−0.8 (0.3)	−0.4 (0.8)
95% CI	(−1.5 to −0.1)	(−1.5 to −0.1)	(−1.8 to 0.9)
P value	.02	.02	.52
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−3.6 (0.3)	−3.5 (0.3)	−4.4 (0.7)
95% CI	(−4.3 to −3.0)	(−4.2 to −2.9)	(−5.7 to −3.1)
P value	<.001	<.001	<.001
HDL cholesterol, %†			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.5 (1.0)	−0.9 (0.8)	1.2 (1.5)
95% CI	(−1.5 to 2.5)	(−2.4 to 0.6)	(−1.8 to 4.2)
P value	.60	.25	.44
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	6.3 (1.0)	3.6 (0.8)	9.5 (1.5)
95% CI	(4.3 to 8.3)	(2.1 to 5.2)	(6.6 to 12.4)
P value	<.001	<.001	<.001
Triglycerides, %†			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−2.6 (2.5)	−1.7 (1.9)	−5.1 (3.5)
95% CI	(−7.5 to 2.2)	(−5.4 to 2.1)	(−12.0 to 1.8)
P value	.29	.38	.15
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−8.5 (2.5)	−5.4 (1.9)	−7.4 (3.4)
95% CI	(−13.4 to −3.7)	(−9.2 to −1.6)	(−14.0 to −0.8)
P value	<.001	.01	.03
Ratio of total cholesterol to HDL cholesterol			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.08 (0.04)	−0.04 (0.03)	−0.10 (0.06)
95% CI	(−0.16 to 0)	(−0.10 to 0.02)	(−0.23 to 0.02)
P value	.05	.23	.11
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.22 (0.04)	−0.15 (0.03)	−0.26 (0.06)
95% CI	(−0.30 to −0.14)	(−0.21 to −0.09)	(−0.38 to −0.13)
P value	<.001	<.001	<.001
Waist circumference, cm			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.2 (0.4)	0.2 (0.3)	−0.5 (0.7)
95% CI	(−1.0 to 0.5)	(−0.5 to 0.8)	(−1.8 to 0.8)
P value	.51	.64	.46
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−2.8 (0.4)	−1.8 (0.3)	−4.0 (0.6)
95% CI	(−3.6 to −2.0)	(−2.4 to −1.1)	(−5.3 to −2.7)
P value	<.001	<.001	<.001
Fasting glucose, mg/dL			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.30 (0.68)	0.37 (0.53)	1.57 (1.11)
95% CI	(−1.63 to 1.03)	(−0.68 to 1.41)	(−0.60 to 3.74)
P value	.66	.49	.16
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.82 (0.68)	−0.26 (0.53)	−0.52 (1.06)
95% CI	(−2.16 to 0.51)	(−1.31 to 0.78)	(−2.60 to 1.56)
P value	.23	.62	.63
Fasting insulin, μIU/mL			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.2 (0.7)	0.3 (0.6)	0.5 (0.9)
95% CI	(−1.2 to 1.7)	(−0.9 to 1.4)	(−1.2 to 2.2)
P value	.77	.65	.58
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−1.8 (0.7)	−1.2 (0.6)	−1.7 (0.8)
95% CI	(−3.3 to −0.4)	(−2.4 to 0)	(−3.4 to −0.1)
P value	.01	.04	.04

(continued)

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Table 3. Placebo-Subtracted Changes From Baseline in Weight and Cardiometabolic Risk Factors for Year 2 for Patients Who Received the Same Treatment in Both Years* (cont)

	Last Observation Carried Forward	Baseline Imputed	Repeated Measures
Insulin resistance derived from homeostasis model assessment			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0 (0.2)	0.1 (0.2)	0.3 (0.2)
95% CI	(−0.4 to 0.5)	(−0.2 to 0.5)	(−0.2 to 0.7)
P value	.84	.46	.24
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.6 (0.2)	−0.3 (0.2)	−0.4 (0.2)
95% CI	(−1.0 to −0.1)	(−0.7 to 0)	(−0.8 to 0)
P value	.01	.05	.08
Systolic blood pressure, mm Hg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.3 (0.7)	0.7 (0.5)	−0.2 (1.1)
95% CI	(−0.1 to 1.6)	(−0.3 to 1.7)	(−2.3 to 1.9)
P value	63	18	.86
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	−0.3 (0.7)	0.1 (0.5)	−0.4 (1.0)
95% CI	(−1.6 to 1.0)	(−0.9 to 1.1)	(−2.4 to 1.6)
P value	.63	.87	.70
Diastolic blood pressure, mm Hg			
5 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.7 (0.4)	0.8 (0.3)	0.5 (0.7)
95% CI	(−0.1 to 1.6)	(0.1 to 1.5)	(−0.9 to 1.8)
P value	.10	.03	.49
20 mg of Rimonabant vs placebo			
Least-squares mean difference (SEM)	0.1 (0.4)	0.2 (0.3)	−0.5 (0.7)
95% CI	(−0.8 to 0.9)	(−0.5 to 0.9)	(−1.8 to 0.8)
P value	.86	.61	.48

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein cholesterol.
SI conversion factors: HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.
*Results shown according to method of imputation. *P* values are for the mean difference between each rimonabant dose and placebo.
†Analyses were performed on percentage changes from baseline.

group continued to receive placebo for year 2. Randomization was balanced within each center and stratified by weight loss (≤2 kg or >2 kg) during the run-in period. Medication compliance, defined as consumption of 80% or greater of tablets, was assessed by tablet counting at each specified visit.

Assessments

Initial screening included a medical history, physical examination, electrocardiography, clinical chemistry, thyroid function, hematology, and urinalysis. Body weight was measured using a calibrated digital or balance scale at screening, biweekly during the run-in period, baseline (randomization), weeks 2 and 4, and then every 4 weeks. Waist circumference was measured using a spring-loaded measuring tape midway between the lower rib and iliac crest and followed the same measurement schedule as body weight.

Fasting serum glucose and insulin levels were measured at screening, baseline, every 12 weeks until week 36, at week 52, every 12 weeks between week 52 and week 88, and at week 104. Serum glucose, insulin, and lipids were assayed according to standard procedures.[15,16] Low-density lipoprotein cholesterol was measured directly by ultracentrifugation. Metabolic syndrome status was assessed according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria[17] at baseline, year 1, and year 2.

Safety Evaluations

Each safety evaluation included a physical examination with collection of vital signs and recording of adverse events. Hematology and serum chemistry were evaluated every 3 months. The hospital anxiety and depression scale,[18] a validated tool for the evaluation of mood and psychological traits that includes depression and anxiety subscales, was assessed at screening, baseline, and at weeks 24, 52, 76, and 104. Electrocardiography screening was performed every 3 months. Adverse events were assessed by spontaneous report at each visit.

Statistical Analysis

Sample Size. The sample size was calculated based on the assumption that the SD of weight change at year 1 would be 10 kg. Thus 2800 randomized patients (560 patients in the placebo group and 1120 patients in each rimonabant dose group [to ensure sufficient patients for rerandomization at the end of year 1]) provided 99% power to detect a 3-kg difference between 1 dose of rimonabant and placebo after 1 year. We chose an α level of .025 to ensure

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

an overall type I error rate of .05 according to a modified Bonferroni procedure.

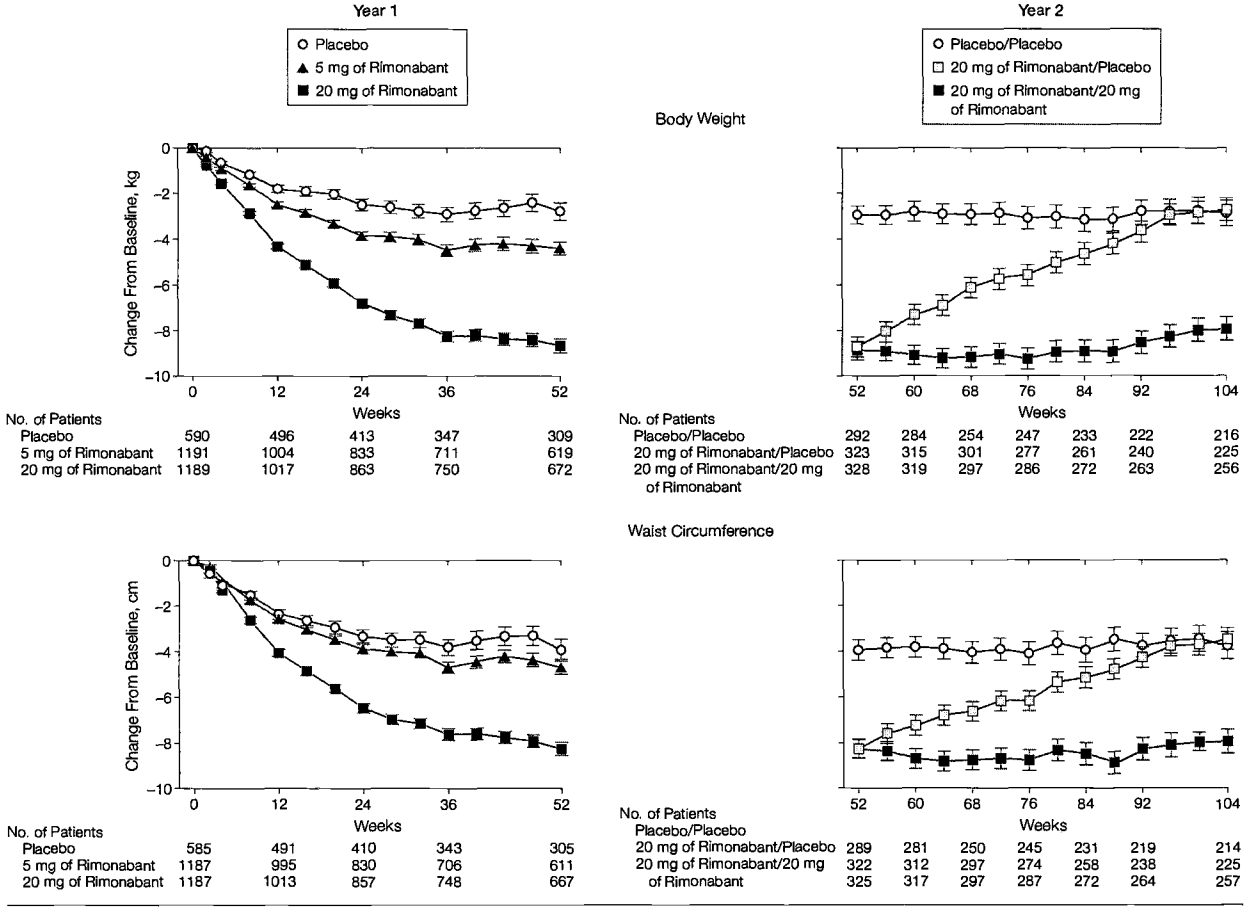
Analysis Populations. Efficacy analyses were performed at the end of years 1 and 2. The 1-year modified intent-to-treat (ITT) population was defined as all randomized patients who received at least 1 dose of the double-blind study drug during the first year and had at least 1 postbaseline trial assessment (TABLE 2 and FIGURE 2). The 2-year modified ITT population for the analysis of the prevention of weight regain was composed of all randomized patients who completed year 1, received at least 1 dose of study drug in year 2, and had at least 1 weight assessment after rerandomization (TABLE 3 and Figure 2). The modified ITT population for the analysis of efficacy over 2 years included patients who received the same double-blind study drug for the entire study (including those who discontinued study participation during the first year).

Primary and Secondary Efficacy Analyses. The primary efficacy variable was weight loss over year 1. The other primary efficacy variable was prevention of weight regain between the first and second years expressed as the change in weight from the end of the first year (rerandomization baseline) to the end of year 2.

Other weight-related criteria were the percentage of patients achieving weight loss of 5% or greater and weight loss of 10% or greater from baseline to years 1 and 2 and changes in waist circumference. Secondary efficacy end points were changes in level of high-density lipoprotein (HDL) cholesterol from baseline to year 1 and the prevalence of the metabolic syndrome. Additional secondary efficacy variables included changes from baseline in systolic and diastolic blood pressure, levels of fasting glucose and insulin, lipids, and insulin resistance measured by homeostasis model assessment[19] (HOMA-IR), which is calculated by multiplying fasting insulin by fasting glucose and dividing by 22.5.

Primary efficacy analyses were applied to the ITT population with the last

Figure 2. Change From Baseline for Body Weight and Waist Circumference Over Years 1 and 2



Error bars indicate SEM

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

observation carried forward (LOCF, FIGURE 3) Comparisons of the primary efficacy end point (weight change from baseline) were conducted using analysis of variance with the modified Bonferroni procedure[20] to adjust for multiple comparisons. The analysis of variance model included treatment and randomization stratum (weight loss of ≤2 kg or >2 kg during the run-in period) as fixed effects. Similar analyses were applied to the secondary efficacy variables Because this analysis excluded repeated measurements made over the course of the study, a post-hoc repeated-measures approach was applied to changes in weight from baseline using a model that included fixed effects (randomization stratum, treatment, days after randomization, and treatment × days interaction) and a random effect for patients. Similar methods were applied to other efficacy end points.

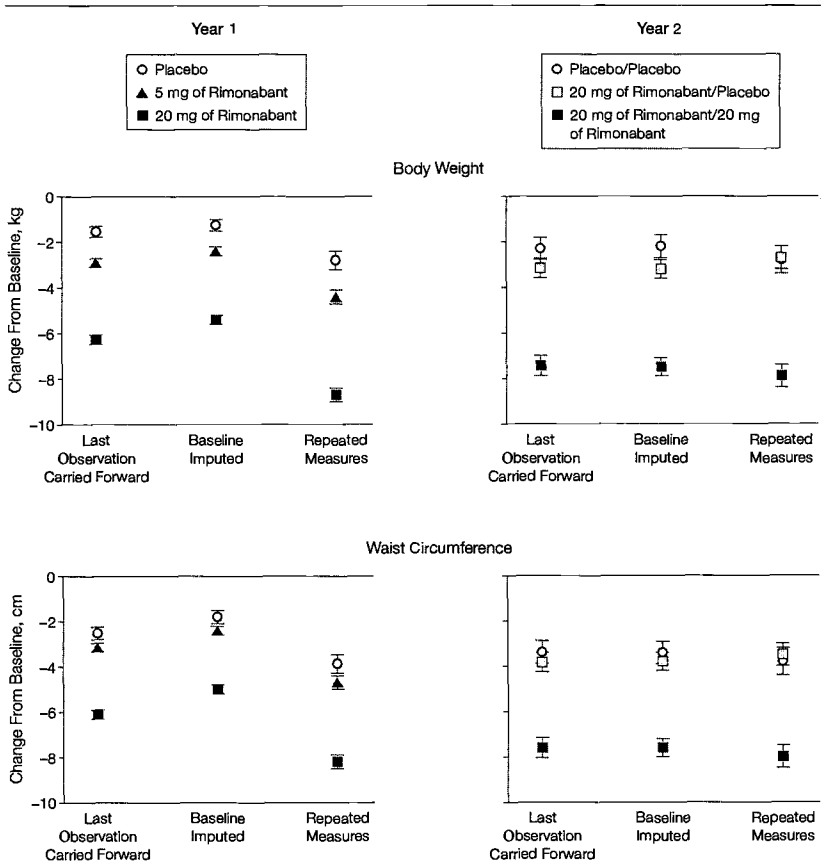
The prevention of weight regain during year 2 was analyzed using a 2-way analysis of covariance model including rerandomization treatment sequence and randomization stratum as fixed effects and weight loss during year 1 as the covariate. Each rerandomized dose group (ie, 20 mg of rimonabant during year 1 and then 20 mg of rimonabant during year 2) was compared with the same dose group that was switched to placebo (ie, 20 mg of rimonabant during year 1 and then placebo during year 2).

As an assessment of sensitivity, a more conservative imputation method than LOCF for handling missing data was applied. For study dropouts with efficacy data and improvement in an end point, the imputed last value was defined as a weighted average of the baseline and LOCF values in which the weights were defined as the proportion of treatment duration during the trial If a study dropout had efficacy data and showed no improvement in an end point, the last value was not imputed because the imputation method would have provided a better result than the LOCF. If a study dropout had no efficacy data, the imputed value was set to the baseline value and the change from baseline was set to zero.

The percentage of patients losing at least 5% or 10% of their baseline body weight in the groups receiving either 20 mg or 5 mg of rimonabant and the percentage of patients meeting the Adult Treatment Panel III criteria[17] for the metabolic syndrome were compared with the percentage of patients receiving placebo using logistic regression.

The estimates of responses in secondary end points to treatment that could not be attributed to weight loss alone were based on standard regression methods in which weight loss (change in weight from baseline to 1 year) was introduced as a covariate (analysis of covariance). The weight-adjusted analysis of covariance model for treatment effect was: $Y=a+\beta T+\gamma W+e$ where Y is the efficacy variable, T is the treatment indicator, and W is weight loss The weight-independent portion of the total treatment effect was calculated as the ratio of the weight-adjusted treatment effect β to the treatment effect $\beta 1$ in the overall unadjusted analysis of variance model $Y=a+\beta 1T+e1$.[21] This ratio reflects the proportion of the total effect size that cannot be explained by weight loss. All statistical tests were 2-sided at the .05 significance level except as noted; all *P* values presented herein are unadjusted. Unless otherwise noted, results are for the ITT population. Statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

Figure 3. Last Observation Carried Forward, Baseline Imputed Measures, and Repeated Measures for Body Weight and Waist Circumference Over Years 1 and 2



Error bars indicate SEM

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

RESULTS

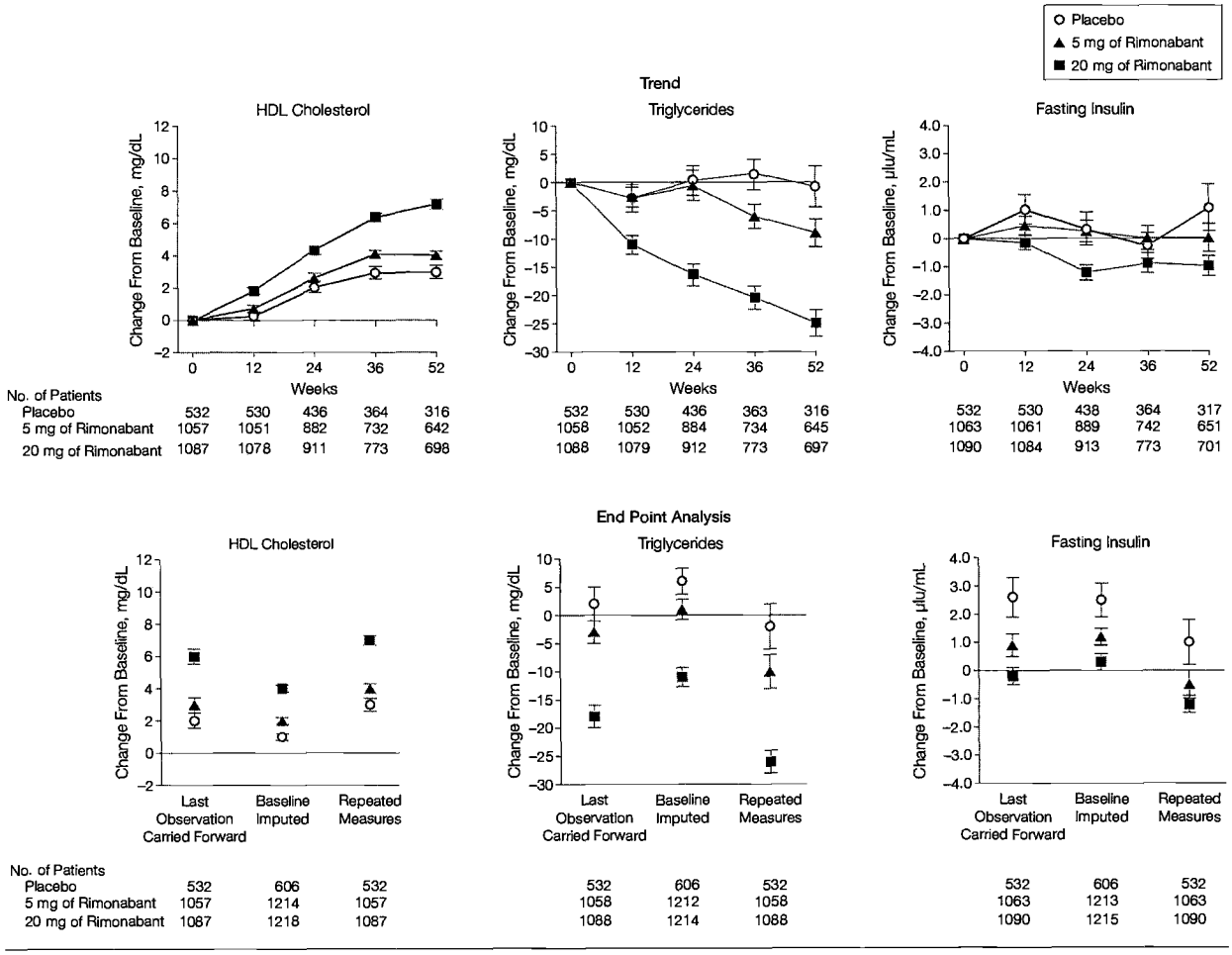
A total of 3045 patients completed the 4-week, placebo run-in and were randomized to double-blind treatment with placebo (n=607), 5 mg of rimonabant (n=1216), or 20 mg of rimonabant (n=1222). Five randomized patients (2 in the group who received 5 mg of rimonabant and 3 in the group who received 20 mg of rimonabant) did not receive double-blind study medication. The disposition of patients over 2 years appears in Figure 1. The characteristics of the study population at randomization were similar in the 3 treatment groups (Table 1).

Year 1 was completed by 51% of patients (n=309) in the placebo group, 51% (n=620) in the 5 mg of rimonabant group, and 55% (n=673) in the 20 mg of rimonabant group. More than 98% of patients receiving rimonabant took more than 80% of the prescribed study medication. There were no differences in compliance between completers and noncompleters. The completion rates for rerandomized patients in year 2 were 72% for patients who received placebo both years, 70% for patients who received 5 mg of rimonabant in year 1 and placebo in year 2, 69% for patients who received 20 mg of rimonabant in year 1 and placebo in year 2, 71% for patients who received 5 mg of rimonabant in both years, and 77% for patients who received 20 mg of rimonabant in both years.

Weight Loss During Year 1

During the 4-week placebo plus diet run-in period, body weight decreased by a mean (SEM) of 1.9 (0.04) kg and waist circumference by 2.1 (0.08) cm. Also during this period, level of HDL cholesterol decreased by a mean (SEM) of 5.8% (0.2%) and level of triglycerides decreased by 1.2% (0.7%). After randomization, weight loss from baseline in the 1-year modified ITT population (Figure 2 and Figure 3) was sig-

Figure 4. Change From Baseline Over Year 1 for Levels of High-Density Lipoprotein (HDL) Cholesterol, Triglycerides, and Fasting Insulin



Error bars indicate SEM. To convert HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

nificantly greater in patients receiving 20 mg or 5 mg of rimonabant than in patients receiving placebo. Similar results were seen when the data were expressed as a placebo-subtracted change from baseline (Table 2). The percentage of patients achieving a 5% or greater weight loss at 1 year was 26.1% for patients receiving 5 mg of rimonabant (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1-1.8; $P=.004$), 48.6% for patients receiving 20 mg of rimonabant (OR, 4.1; 95% CI, 3.2-5 2, $P< 001$), and 20.0% for patients receiving placebo. The percentage of patients achieving a 10% or greater weight loss was 25.2% for patients receiving 20 mg of rimonabant and 8.5% for patients receiving placebo (OR, 4 0; 95% CI, 2 9-5.5; $P<.001$). However, only 10.6% of patients receiving 5 mg of rimonabant achieved a 10% or greater weight loss (OR, 1.3; 95% CI, 0.9-1.8). Compared with the patients receiving placebo, waist circumference decreased more in the patients receiving 20 mg of rimonabant (Figure 2 and Figure 3).

Weight Loss During Year 2

The 2-year modified ITT population that was previously treated with 20 mg of rimonabant continued treatment with 20 mg of rimonabant and maintained a mean (SEM) weight loss from baseline of 7 4 (0.4) kg whereas the participants who were rerandomized to placebo regained most of their previous weight loss (Figure 2 and Figure 3). A similar pattern was seen for waist circumference.

Weight Loss in Patients Receiving the Same Treatment for 2 Years

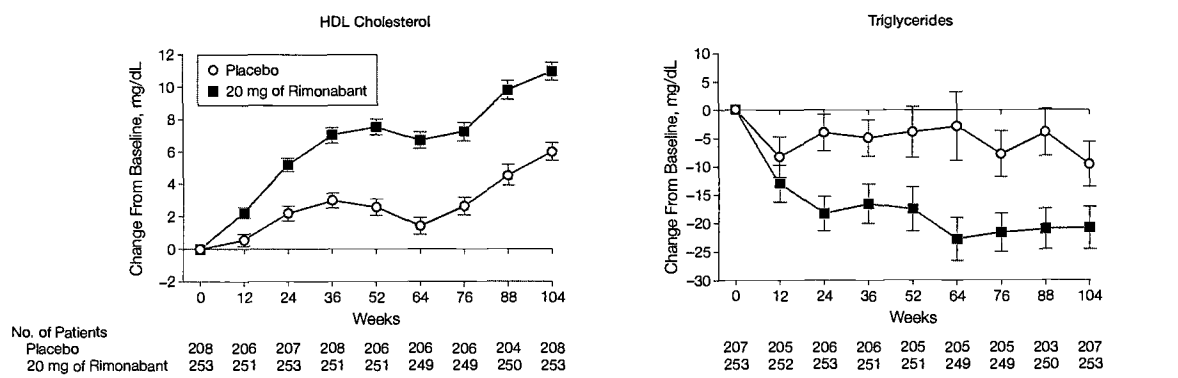
Compared with patients receiving placebo, cumulative weight loss was significantly greater in patients receiving 20 mg of rimonabant in both years (but not in those receiving 5 mg of rimonabant in both years) (Table 3). A greater percentage of patients receiving 20 mg of rimonabant achieved a weight loss of 5% or greater (40% vs 19% of patients receiving placebo, OR, 2.9 [95% CI, 2.3-3 7], $P<.001$) and 10% or greater (17% vs 8% of patients receiving placebo, OR, 2.3 [95% CI, 2.1-3.3]; $P<.001$). The 2-year mean (SEM) change from baseline in waist circumference was also significantly greater in patients receiving 20 mg of rimonabant (−5.0 [0 2] cm) compared with patients receiving placebo (−2 2 [0.3] cm, $P<.001$).

Cardiometabolic Risk Factors During Year 1

Levels of HDL cholesterol increased and fasting insulin levels decreased in patients receiving either 5 mg or 20 mg of rimonabant. Levels of triglycerides decreased in patients receiving 20 mg of rimonabant but not in patients receiving 5 mg of rimonabant (Table 2 and FIGURE 4). The prevalence of the metabolic syndrome according to Adult Treatment Panel III criteria significantly declined in patients receiving 20 mg of rimonabant (from 34.8% to 21.2%) compared with patients receiving placebo (31.7% to 29.2%; $P<.001$). Levels of total cholesterol and low-density lipoprotein cholesterol were not significantly different among the 3 groups (data available on request). Insulin resistance estimated by the HOMA-IR increased in patients receiving placebo but not in patients receiving 20 mg of rimonabant. Systolic and diastolic blood pressures tended to decrease slightly but not significantly in patients receiving either 5 mg or 20 mg of rimonabant (Table 2).

In patients receiving 20 mg of rimonabant, the observed effects at 1 year in levels of HDL cholesterol, triglycerides, fasting insulin, and in HOMA-IR were approximately twice that attributable to the concurrent weight loss alone using analysis of covariance. For example, of the observed 7 2% increase in level of HDL cholesterol in patients receiving 20 mg of rimonabant, there was only a 4 2% increase in level of HDL cholesterol after adjustment for weight loss ($P< 001$). The residual effects after weight-loss adjustment in patients receiving 20 mg of rimonabant were 47% of observed effects for triglycerides ($P= 008$); 50% of observed effects for fasting insulin ($P=.04$); and

Figure 5. Change in the Completers Population From Baseline Over Years 1 and 2 for Levels of High-Density Lipoprotein (HDL) Cholesterol and Triglycerides



Error bars indicate SEM. To convert HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Table 4. Safety Data, Adverse Events, and Hospital Anxiety and Depression Scores*

		Rimonabant	
	Placebo (n = 607)	5 mg (n = 1214)	20 mg (n = 1219)
Safety Data for Year 1†‡			
Overall drop-out rate	298 (49 1)	595 (49 0)	547 (44 9)
Adverse event			
Any	498 (82.0)	1013 (83.4)	1042 (85.5)
Serious§	21 (3.5)	46 (3.8)	55 (4.5)
Discontinued study due to adverse event	44 (7.2)	114 (9.4)	156 (12.8)
Psychiatric disorder	14 (2.3)	44 (3.6)	76 (6.2)
Depressed mood‖	8 (1 3)	25 (2 1)	27 (2.2)
Anxiety	2 (0.3)	7 (0.6)	12 (1.0)
Irritability	0	2 (0 2)	6 (0.5)
Insomnia	1 (0.2)	1 (<0 1)	6 (0.5)
Nervous system	6 (1 0)	14 (1.2)	27 (2.2)
Headache	2 (0.3)	4 (0 3)	6 (0.5)
Dizziness	1 (0.2)	0	9 (0 7)
Gastrointestinal tract	4 (0 7)	8 (0 7)	20 (1 6)
Nausea	1 (0.2)	2 (0 2)	11 (0 9)
Adverse Events‡			
	(n = 498)	(n = 1013)	(n = 1042)
Upper respiratory tract infection	76 (15.2)	163 (16 1)	193 (18.5)
Nasopharyngitis	70 (14 0)	163 (16 1)	177 (17 0)
Nausea	29 (5 8)	69 (6 8)	117 (11 2)
Arthralgia	41 (8 2)	88 (8 7)	92 (8 8)
Sinusitis	58 (11 7)	88 (8 7)	91 (8 7)
Headache	51 (10 2)	92 (9 1)	81 (7 8)
Back pain	30 (6 1)	71 (7 0)	61 (5 9)
Influenza	38 (7 7)	76 (7 5)	92 (8 8)
Diarrhea	25 (5 1)	73 (7 2)	55 (5 3)
Gastroenteritis viral	24 (4 8)	49 (4 8)	59 (5 7)
Dizziness	20 (4 0)	46 (4 5)	58 (5 6)
Anxiety	10 (2 1)	33 (3 3)	64 (6 1)
Bronchitis	25 (5 1)	48 (4 7)	45 (4 3)
Depressed mood	15 (3 1)	42 (4 1)	54 (5 2)
Fatigue	18 (3 6)	38 (3 8)	54 (5 2)
Insomnia	22 (4 4)	30 (3 0)	60 (5 8)
Hospital Anxiety and Depression Scores			
	(n = 490)	(n = 991)	(n = 1026)
Depression subscore, mean (SD)			
Baseline	3 0 (2 7)	3 0 (2 8)	2 9 (2 8)
Last value during year 1	3 1 (3 2)	3 0 (3 2)	3 0 (3 2)
Change	0 1 (2 8)	0 (2 8)	0 1 (3 0)
Anxiety score, mean (SD)			
Baseline	5 0 (3 2)	5 0 (3 3)	4 8 (3 1)
Last value during year 1	5 2 (3 6)	5 3 (3 7)	5 6 (3 9)
Change	0 2 (3 0)	0 3 (2 9)	0 9 (3 3)

*Values are expressed as number (percentage) unless otherwise indicated. Additional data available on request.
†One patient may report several events. Onset date during treatment exposure and up to 75 days following the last study drug intake.
‡Coded using MedDRA (version 7 0) to a preferred term and associated primary system organ class and made consistent between patients by the use of a standard preferred term that belongs to a single primary system organ class.
§Two deaths were reported in the 5-mg rimonabant group: 1 male patient was found dead by gunshot and 1 female patient with a history of long QT syndrome died from cardiac arrest. In the RIO program (n = 6625), the deaths were equally distributed across groups (4 in the placebo group, 3 in the 5-mg rimonabant group, and 4 in the 20-mg rimonabant group).
‖Consisted of depression, major depression, depressed mood, and depressive symptoms.

51% of observed effects for HOMA-IR (P = 07)

Cardiometabolic Risk Factors in Year 2

Compared with patients who continued to receive 5 mg or 20 mg of rimonabant, patients who were rerandomized to placebo in year 2 had increased levels of triglycerides and decreased levels of HDL cholesterol (data available on request). In the patients who completed the study and who were treated with either placebo or 20 mg of rimonabant for 2 years, levels of HDL cholesterol continued to increase from baseline during year 2 but significantly so in patients who were treated with 20 mg of rimonabant ($P<.001$, FIGURE 5). Compared with patients receiving placebo, both levels of triglycerides and the prevalence of the metabolic syndrome declined more from baseline in patients receiving 20 mg of rimonabant ($P<.001$).

Safety and Tolerability

The percentage of patients reporting at least 1 adverse event was similar across treatment groups (85.5% for patients receiving 20 mg of rimonabant, 83.4% for patients receiving 5 mg of rimonabant, and 82.0% for patients receiving placebo, TABLE 4). Compared with patients receiving placebo, the overall incidence of adverse events leading to study withdrawal in year 1 was slightly higher in patients receiving 5 mg of rimonabant and even greater in patients receiving 20 mg of rimonabant, mainly due to psychiatric, nervous system, and gastrointestinal tract adverse events. Compared with patients receiving placebo, adverse events (upper respiratory tract infection, nasopharyngitis, nausea, influenza, diarrhea, arthralgia, anxiety, insomnia, viral gastroenteritis, dizziness, depressed mood, and fatigue) were reported in 5% or greater of patients receiving 20 mg of rimonabant. There were no differences among the treatment groups in changes over time in corrected QT interval and either the anxiety or

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

depression subscales of the hospital anxiety and depression scale.

In year 2, the overall rates of adverse events, study withdrawals, and adverse event–related study withdrawals were lower than in year 1; there were no differences in overall rates among the treatment groups (TABLE 5). Upper respiratory tract infection, nasopharyngitis, or influenza occurred in 5% or greater of patients receiving either 5 mg or 20 mg of rimonabant at year 2 and overall were more frequent in rimonabant-treated patients for both years.

Table 5. Adverse Events in Patients Who Received the Same Treatment in Both Years

	No. (%) of Patients		
		Rimonabant	
	Placebo (n = 298)	5 mg (n = 300)	20 mg (n = 333)
Adverse event*			
Any	246 (82.6)	243 (81.0)	276 (82.9)
Serious	14 (4.7)	18 (6.0)	13 (3.9)
Discontinued study due to adverse event	12 (4.0)	19 (6.3)	14 (4.2)
Psychiatric disorder	4 (1.3)	6 (2.0)	7 (2.1)
Depressed mood†	3 (1.0)	4 (1.3)	4 (1.2)
Anxiety	0	1 (0.3)	2 (0.6)
Upper respiratory tract infection	44 (14.8)	53 (17.7)	55 (16.5)
Nasopharyngitis	47 (15.8)	41 (13.7)	64 (19.2)
Sinusitis	27 (9.1)	23 (7.7)	25 (7.5)
Arthralgia	29 (9.7)	25 (8.3)	20 (6.0)
Back pain	20 (6.7)	21 (7.0)	17 (5.1)
Influenza	22 (7.4)	12 (4.0)	25 (7.5)
Bronchitis	11 (3.7)	25 (8.3)	11 (3.3)
Extremity pain	9 (3.0)	15 (5.0)	12 (3.6)

*One patient may report several events. Onset date during treatment exposure and up to 75 days following the last study drug intake. Coded using MedDRA (version 7.0) to a preferred term and associated primary system organ class and made consistent between patients by the use of a standard preferred term that belongs to a single primary system organ class.
†Consisted of depression, major depression, depressed mood, and depressive symptoms.

COMMENT

Rimonabant, the first selective cannabinoid-1 receptor blocker to enter clinical trials, was tested in a randomized, double-blind, placebo-controlled 2-year multicenter study. The results suggest that 20 mg/d of rimonabant is effective in reducing body weight and waist circumference, while also favorably affecting several cardiometabolic risk factors. Most of these effects were dose-dependent. Furthermore, the differences in the patients receiving 20 mg of rimonabant compared with patients receiving placebo in levels of HDL cholesterol, triglycerides, fasting insulin, and HOMA-IR appeared to exceed that expected from the weight loss achieved. These findings support and extend results from other randomized controlled trials of rimonabant therapy.[22,23]

RIO-North America addressed the efficacy and safety profile of rimonabant over 1 year, the long-term effectiveness of rimonabant in preventing weight regain; and the efficacy and tolerability of continuous long-term rimonabant treatment over 2 years. Clinically significant weight loss achieved during year 1 was well maintained during year 2 in patients receiving 20 mg of rimonabant during both years. When patients treated with 5 mg or 20 mg of rimonabant at year 1 were rerandomized to placebo in year 2, they regained a substantial amount of the weight they had lost. However, body weight still remained slightly lower in these patients than in the patients treated with placebo for 2 years. These findings highlight the concept that sustained weight loss and associated favorable changes in cardiometabolic risk factors require continuous long-term treatment as seen in other chronic disorders, such as diabetes and hypertension in which treatment is effective only for as long as patients are receiving therapy.

Compared with patients who received placebo, patients who received 20 mg of rimonabant had favorable changes in levels of HDL cholesterol, triglycerides, and fasting insulin and in HOMA-IR that appeared to be approximately twice that expected from the achieved weight loss alone, suggesting a direct pharmacological effect of rimonabant on glucose and lipid metabolism beyond the weight loss achieved. In patients who received 20 mg of rimonabant, levels of HDL cholesterol increased continuously throughout the 2-year study whereas body weight stabilized, further supporting a direct pharmacological effect not attributable to weight loss alone. Preclinical studies indicate that rimonabant increases adiponectin gene expression and production in adipose tissue,[11] increases insulin-mediated glucose uptake in isolated soleus muscle,[12] and that cannabinoid-1 receptor antagonism or deletion decreases de novo hepatic fatty acid synthesis and lipid accumulation in response to the consumption of high-fat foods.[9] Patients with the metabolic syndrome who have insulin resistance have multiple defects in glucose and lipid metabolism associated with excess intraabdominal fat, hypoadiponectinemia, and high levels of cytokines and adhesion molecules.[24] While further study is needed to elucidate the specific mechanisms underlying the apparent direct action of rimonabant on lipid and glucose metabolism, these effects may be mediated by adiponectin and reduction of abdominal obesity.[23,25]

Rimonabant significantly reduced waist circumference, a measure of abdominal adiposity, and the prevalence of the metabolic syndrome. A recent study[26] showed that measured intraabdominal fat was independently associated with all 5 of the metabolic syndrome criteria, suggesting that it may have a central pathophysiological role

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Moreover, multivariable analyses indicated that waist circumference and level of triglycerides together might be a useful surrogate marker for measured insulin resistance and intraabdominal adiposity in individuals without diabetes. Furthermore, fasting insulin and waist circumference predicted insulin sensitivity measured directly by the hyperinsulinemic euglycemic clamp and intraabdominal fat measured by computed tomography. These results suggest that fasting insulin level and waist circumference are reliable indicators of high-risk patients in clinical practice. In the context of the current obesity epidemic and the associated burden on health care resources, clinical tools such as waist circumference may enable physicians to identify those patients at high risk for type 2 diabetes and cardiovascular disease, who may benefit from early intervention to improve their cardiometabolic risk status.

Rimonabant was generally well tolerated with adverse effects that were mostly mild and moderate In patients receiving the same treatment for 2 years, the study withdrawal rate due to adverse events became comparable among all patients during year 2, suggesting that the adverse effects occur early and that 5 mg/d and 20 mg/d of rimonabant have a comparable safety and tolerability profile with placebo.

There are several limitations to our study. The low retention rates of only about 50% in all treatment groups, while consistent with previous studies in overweight or obese patients,[27] present a major challenge in data analysis and interpretation. The use of the LOCF approach to impute missing values assumes that individual data at the time of dropout are representative of data at the end of the study if the participant had completed the study [28] The results of the study also may be affected by participants who derived less benefit and dropped out more frequently Moreover, data from patients who completed the study may not be representative of the overall study population when the drop-out rate is high. However, sensitivity analyses, including a repeated-measures approach and an imputation of final values adjusted for duration of participation, supported the conclusions of the LOCF analysis. Other factors that may diminish the generalizability of the study results include the limited racial diversity and the overall predominance of white women in the study. Lastly, larger studies are necessary to assess less frequent adverse events and longer duration studies will be needed to confirm the long-term safety of rimonabant beyond 2 years.

In conclusion, in the RIO-North America trial, 20 mg of rimonabant plus a standard dietary intervention produced sustained, clinically meaningful weight loss and favorable changes in cardiometabolic risk factors over 1 year and prevented weight regain in year 2 with favorable effects compared with placebo on fasting serum levels of HDL cholesterol and triglycerides and HOMA-IR. Compared with patients who had received 20 mg of rimonabant in year 1 and were then reassigned to receive placebo in year 2, those treated with 20 mg of rimonabant for 2 years maintained weight loss and differences from patients receiving placebo in multiple cardiometabolic risk factors, reflecting the potential effectiveness of long-term rimonabant therapy. It must be acknowledged that the trial was limited by a high drop-out rate and that long-term effects of the drug require further study. Still, our observations collectively suggest that rimonabant may well represent an innovative approach to the management of multiple cardiometabolic risk factors, facilitating and maintaining improvements through weight loss–dependent and –independent pathways.

Author Affiliations: Obesity Research Center, St Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY (Dr Pi-Sunyer), Department of Medicine, Cornell Weil Medical College, New York, NY (Dr Aronne), Sanofi-Aventis, Malvern, Pa (Dr Heshmati and Ms Devin), and Dallas Diabetes and Endocrine Center, Dallas, Tex (Dr Rosenstock).

Author Contributions: Dr Pi-Sunyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pi-Sunyer, Aronne, Heshmati.
Acquisition of data: Pi-Sunyer, Aronne, Heshmati, Rosenstock.
Analysis and interpretation of data: Pi-Sunyer, Aronne, Heshmati, Devin, Rosenstock.
Drafting of the manuscript: Pi-Sunyer, Aronne.
Critical revision of the manuscript for important intellectual content: Aronne, Devin, Rosenstock.
Statistical analysis: Devin.
Obtained funding: Pi-Sunyer.
Administrative, technical, or material support: Pi-Sunyer, Heshmati, Rosenstock.
Study supervision: Aronne, Heshmati, Rosenstock.
Financial Disclosures: Drs Pi-Sunyer and Aronne have received honoraria from Sanofi-Aventis for speaker's presentations. No other authors reported financial disclosures.
Funding/Support: RIO-North America was supported by a research grant from Sanofi Synthelabo Research, a division of Sanofi Synthelabo Inc, a member of the Sanofi-Aventis group.
Role of the Sponsor: Sanofi-Aventis participated in discussions regarding study design and protocol development and the sponsor provided logistical support for the trial, data collection, and data analysis, and helped in preparing the manuscript. The sponsor was permitted to review the manuscript, but the final decision on content was with the corresponding author in conjunction with the other authors.
Independent Statistical Review: All study data were transferred from Sanofi-Aventis to the Department of Medicine at St Luke's-Roosevelt Hospital Center for independent reanalysis by Stanley Heshka, PhD. Statistical reanalyses of the raw data were performed by Dr Heshka. There were no discrepancies between the reanalysis and the original interpretation of the results and conclusions. In lieu of financial compensation for Dr Heshka's time and effort in performing the statistical analyses, an unrestricted educational grant from Sanofi-Aventis was given to the Obesity Research Center at St Luke's-Roosevelt Hospital Center in New York, NY.
Data and Safety Monitoring Board: Alain Leizorovicz, MD (chairman), Université Claude Bernard, Lyon, France, Michael Weintraub, MD, University of Rochester School of Medicine and Dentistry, Rochester, NY, Jean-Louis Imbs, MD, Hôpital Civil, Strasbourg, France, Elliot Danforth, MD, University of Vermont, Burlington, David P L Sachs, MD, Palo Alto Center for Pulmonary Disease, Palo Alto, Calif.
RIO North America Investigators: *Canada (Ontario).* Denis Callaghan, Hamilton, Jeff Daiter, Richmond Hill, John Nuttall, Kingston, William O'Mahony, Corunna, Duncan Sinclair, Aylmer; Donald Spink, Peterborough, Paul Willoughby, Woodstock; Paul Ziter, Windsor. *United States:* Andrew Ahmann, Portland, Ore, James Anderson, Lexington, Ky; Louis Aronne, New York, NY, Richard Atkinson, Madison, Wis, Michael Basista, Bloomfield, NJ, Kathleen Baskett, Missoula, Mont; Harold Bays, Louisville, Ky; Gregory Bishop, San Diego, Calif; Scott Bleser, Bellbrook, Ohio; Marshall Block, Phoenix, Ariz; Stephen Brady, Naples, Fla, Ronald Brazg, Renton, Wash; Robert Call, Richmond, Va, Antonio Caos, Ocoee, Fla, Harry Collins, South Plainfield, NJ; Gordon Connor, Birmingham, Ala, Martin Conway, Albuquerque, NM, Lydia Corn, Sarasota, Fla, Walter Dunbar, Atlanta, Ga, Ronald Emkey, Wyomissing, Pa, James Ferguson, Salt Lake City, Utah; Harold Fleming, Spartanburg, SC, Nicholas Fleming, Spartanburg, SC, Arthur Frank, Washington, DC; Ken Fujioka, San Diego, Calif; Sidney Funk, Atlanta, Ga, Elizabeth Gallup, Overland Park, Kan, W Thomas Garland, Lawrenceville, NJ, Jeffrey Geohas, Chicago, Ill; Eric Goldberg, West Palm Beach, Fla, Frank Greenway, Baton Rouge, La, Paula Hall, Indianapolis, Ind, Wayne Harper, Raleigh, NC; Scott Horn, San Antonio, Tex; Roy Kaplan, Concord, Calif; Richard Krause, Chattanooga, Tenn, Diane Krieger, Miami, Fla, Roberta Loeffler, Wichita, Kan, Barry Lubin, Norfolk, Va, Thomas Marbury, Orlando, Fla, Clark McKeever, Hous-

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

ton, Tex, James McKenney, Richmond, Va, Curtis Mello, Swansea, Mass, Neerja Misra, Lawrenceville, NJ, Patrick O'Neil, Charleston, SC, F Xavier Pi-Sunyer, New York, NY, David Podlecki, Longmont, Colo, Gary Post, Highlands Ranch, Colo, R Walter Powell, Newark, Del, Stephen Rafelson, Langhorne, Pa, Kenneth Rictor, Scotland, Pa, Julio Rosenstock, Dallas, Tex, Daniel Rowe, West Palm Beach, Fla, John Rubino, Raleigh, NC, Donald Schumacher, Charlotte, NC, Douglas Schumacher, Columbus, Ohio, Howard Schwartz, Miami, Fla, Simona Scumpia, Austin, Tex, Stephan Sharp, Nashville, Tenn, Earl Shrago, Madison, Wis, Diane Smith, Augusta, Ga, Norman Soler, Springfield, Ill, Paul Tung, Dover, NH, Greggory Volk, Beavercreek, Ohio, Ralph Wade, Salt Lake City, Utah, Richard Weinstein, Walnut Creek, Calif, Todd Wine, Oceanside, Calif, Lisa Wright, Birmingham, Ala, John Zerbe, Cincinnati, Ohio, Douglas Zmolek, Manlius, NY

Previous Presentation. Presented in part at the American Heart Association's Scientific Sessions, New Orleans, La, November 7-10, 2004.

Acknowledgment: We appreciate the expert assistance of Stanley Heshka, PhD (St Luke's-Roosevelt Hospital Center, Columbia University, New York, NY) in conducting an independent statistical analysis of the study data and in providing guidance on appropriate statistical methods.

REFERENCES

1 Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA*. 2004;291:2847-2850.

2. Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2004, 110:2952-2967.

3 Solomon CG, Manson JE. Obesity and mortality: a review of the epidemiologic data. *Am J Clin Nutr*. 1997;66:1044S-1050S.

4. National Institutes of Health Expert Panel on the Identification Evaluation and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obes Res*. 1998, 6(suppl 2):51S-209S.

5 Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990;346:561-564.

6. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365:61-65.

7 Howlett AC. The cannabinoid receptors. *Prostaglandins Other Lipid Mediat*. 2002;68:619-631.

8. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest*. 2003,112:423-431.

9 Osei-Hyiaman D, DePetrillo M, Pacher P, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest*. 2005,115:1298-1305.

10. Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature*. 2001;410:822-825.

11. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol*. 2003;63:908-914.

12. Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. *Int J Obes (Lond)*. 2005;29:183-187.

13. Ravinet Trillou C, Arnone M, Delgorge C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol*. 2003,284:R345-R353.

14. Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism in Man*. Washington, DC: Carnegie Institute of Washington, 1919. Publication 279.

15. Jacobs D, DeMott W, Grady H, Horvat R, Huestis D, Kasten B, eds. *Laboratory Test Handbook*. 4th ed. Cleveland, Ohio: Lexi-Comp Inc; 1996.

16. Rifai N, Warnick G, eds. *Laboratory Measurement of Lipids, Lipoproteins, and Apolipoproteins*. Washington, DC: AACC Press; 1994.

17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.

18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-370.

19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.

20. Hochberg Y. A sharper Bonferonni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-802.

21. Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. *Biometrics*. 1998;54:1014-1029.

22. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*. 2005;365:1389-1397.

23. Despres JP, Golay A, Sjostrom L, Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med*. 2005;353:2121-2134.

24. Salmenniemi U, Ruotsalainen E, Pihlajamaki J, et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. *Circulation*. 2004,110:3842-3848.

25. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab*. 2002,13:84-89.

26. Carr DB, Utzschneider KM, Hull RL, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004, 53:2087-2094.

27. Padwal R, Li S, Lau D. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obes Relat Metab Disord*. 2003;27:1437-1446.

28. Gadbury GL, Coffey CS, Allison DB. Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. *Obes Rev*. 2003;4:175-184.

©2006 American Medical Association. All rights reserved.

Downloaded from www.jama.com on November 30, 2007

Exhibit D

NYPL RESEARCH LIBRARIES
3 3433 07629428 3
Case 1:07-cv-10279-GBD Document 23-6 Filed 06/30/2008 Page 2 of 16
DELIVERY DESK & JSP 90-258 SIBL
The Lancet. v. 368 no. 9548 Nov 11-17, 2006

THE LANCET
www.thelancet.com

"What is the commonest cause of death in a child with diabetes? The answer—from a global perspective—is lack of access to insulin"

See Comment page 1626

N.Y.P.L.
LAU/0645/03356778-5/S/LAD 01 00/001
SCIENC, IND. & BUSIN/LANCET11 0217
NEW YORK PUBLIC LIBRARY
BRAND CENTRAL STATION
PO BOX 2233 NY 10163 2233
SCH 3-DIGIT 100

Articles
Mortality from diseases associated with high blood glucose
See page 1651

Articles
Rimonabant for overweight or obese patients with type 2 diabetes
See page 1660

Articles
Reduction in incidence of type 2 diabetes by lifestyle intervention
See page 1673

Review
Obesity and type 2 diabetes in Asia
See page 1681

New Drug Class
Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes
See page 1696

THE LANCET

Volume 368 · Number 9548 · November 11, 2006

The Lancet—London
32 Jamestown Road
London NW1 7BY
UK
T +44 (0)20 7424
F +44 (0)20 7424
The Lancet—New York
360 Park Avenue South
New York, NY 10010
USA
T +1 212 633 381
F +1 212 633 385
editorial@lancet.com

Rhona MacDonald
Zoë Mullan
Joanna Palmer
Richard Turner
North American Editor
Michael McCarthy (Seattle)
T +1 206 706 7461
North American Senior Editors
Faith McLellan (New York)
Maja Zecevic (New York)
European Associate Editor
Patricia Schlagenhauf
T +41 1 362 7604
Senior Assistant Editors
Information for Authors
Guidelines for authors

Editorial

1623 Change at the Rockefeller Foundation (W)

1624 Climate change preparations must focus on health disparities

1624 Tackling the threat to health of diabetes mellitus

Comment

1625 Diabetes fights for recognition
P Lefèbvre, M Silink

1626 Dying of diabetes
E A M Gale

1628 Diabetes care in Africa
J C Mbanya and others

1629 Challenging the future: the Global Prevention Alliance
N Rigby, K Baillie

1631 Blood glucose levels: facing a global crisis
M Avendano, J P Mackenbach

1632 Does rimonabant pull its weight for type 2 diabetes? (W)
S J Cleland, N Sattar

1634 Lifestyle interventions to prevent type 2 diabetes
R B Goldberg

1636 Apostrophe catastrophe
D McNamee

World Report

1637 Landmines pose further danger to Uganda's war refugees
W Wakabi

1639 Does the world need another AIDS authority?
D Billingham

Perspectives

1641 Web: Bloggers beware: conflicts of interest and diabetes
I Oransky

1642 In brief
M Larkin

1643 Profile: Paul Zimmet: fighting the "diabesity" pandemic
S Pincock

Obituary

1644 Sir Philip Randle
H Brown

Correspondence

1645 Effect of obesity in patients with coronary artery disease
J Garvey, W T McNicholas; C M Schooling and others; A Romero-Corral and others

1646 Pneumonia and child mortality
S R C Howie, R A Adegbola; K Ahmed

1647 Highly active antiretroviral therapy and HIV transmission
A E Grulich; J Montaner

1648 Compliance with treatment for osteoporosis
A Cooper

1648 HIV/AIDS vulnerability of Nepali migrants to India: whose concern?
K C Poudel and others

1648 Effective implementation of the Human Tissue Act
J Ironside

1649 Dapoxetine for treatment of premature ejaculation
R K R Salokangas; J L Pryor

1650 Scientific publications and the developing world
M R Mohebbi

1650 **Department of Error**

Articles

1651 Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration
G Danaei and others

1660 ➔(W) Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes
A J Scheen and others

1673 Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention
J Lindström and others

Clinical Picture

1680 Malignant melanoma of the external ear canal
S A Hannan, A Parikh

Review

1681 Epidemic obesity and type 2 diabetes in Asia
K-H Yoon and others

1689 Diabetes care in sub-Saharan Africa
D Beran, J S Yudkin

New Drug Class

1696 The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes
D J Drucker, M A Nauck

Series

1706 (W) Sexual and Reproductive Health 2
Sexual behaviour in context: a global perspective
K Wellings and others

1729 (W) Health System Reform in Mexico 3
Benchmarking of performance of Mexican states with effective coverage
R Lozano and others

Case Report

1742 Suppurative thyroiditis
B Dunham and others

➔ Peer reviewed and fast-tracked to publication in 4 weeks

(W) Previously published online

See www.thelancet.com for WebExtra content

International Advisory Board
Karen Antman (Boston)
Valerie Beral (Oxford)
Robert Beaglehole (Geneva)
Robert Fletcher (Boston)
Suzanne Fletcher (Boston)
Karen Gelmon (Vancouver)
Johan Giesecke (Stockholm)
David Grimes (Durham)
Jay Levy (San Francisco)
Sue Lightman (London)
Judith Lumley (Melbourne)
Elizabeth Molyneux (Blantyre)
Alwyn Mwinga (Lusaka)
Marie-Louise Newell (London)
Magne Nylenna (Oslo)
Stuart Pocock (London)
Giuseppe Remuzzi (Bergamo)
Ken Schulz (Chapel Hill)
Frank Shann (Melbourne)
Anne Tattersfield (Nottingham)
Chris Van Weel (Nijmegen)
Jan Vandenbroucke (Leiden)
David Weatherall (Oxford)
Nick White (Bangkok)

Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

*André J Scheen, Nick Finer, Priscilla Hollander, Michael D Jensen, Luc F Van Gaal, for the RIO-Diabetes Study Group**

Lancet 2006; 368: 1660–72

Published Online October 27, 2006 DOI:10.1016/S0140-6736(06)69571-8

See Comment page 1632

*Group members listed at end of report

Division of Diabetes, Nutrition and Metabolic Disorders, CHU Sart Tilman, University of Liege, Liege, Belgium (Prof A J Scheen MD); **Department of Medicine, School of Clinical Medicine, University of Cambridge, Cambridge, UK** (Prof N Finer MD); **Ruth Collins Diabetes Center, Baylor University Medical Center, Dallas, TX, USA** (Prof P Hollander MD); **Endocrine Research Unit, Mayo Clinic, Rochester, MN, USA** (Prof M D Jensen MD); **and Department of Diabetology, Metabolism and Clinical Nutrition, Antwerp University Hospital, Antwerp, Belgium** (Prof L F Van Gaal MD)

Correspondence to: Prof A J Scheen, Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman (B35), B 4000 Liege, Belgium **andre.scheen@chu.ulg.ac.be**

Summary

Background **Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients. The aim of the RIO-Diabetes trial was to assess the efficacy and safety of rimonabant in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylureas.**

Methods **1047 overweight or obese type 2 diabetes patients (body-mass index 27–40 kg/m²) with a haemoglobin A_{1c} (HbA_{1c}) concentration of 6·5–10·0% (mean 7·3% [SD 0·9] at baseline) already on metformin or sulphonylurea monotherapy were given a mild hypocaloric diet and advice for increased physical activity, and randomly assigned placebo (n=348), 5 mg/day rimonabant (360) or 20 mg/day rimonabant (339) for 1 year. Two individuals in the 5 mg/day group did not receive double-blind treatment and were thus not included in the final analysis. The primary endpoint was weight change from baseline after 1 year of treatment. Analyses were done on an intention-to-treat basis. This trial is registered at ClinicalTrials.gov, number NCT00029848.**

Findings **692 patients completed the 1 year follow-up; numbers in each group after 1 year were much the same. Weight loss was significantly greater after 1 year in both rimonabant groups than in the placebo group (placebo: –1·4 kg [SD 3·6]; 5 mg/day: –2·3 kg [4·2], p=0·01 *vs* placebo; 20 mg/day: –5·3 kg [5·2], p<0·0001 *vs* placebo). Rimonabant was generally well tolerated. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group, mainly due to depressed mood disorders, nausea, and dizziness.**

Interpretation **These data indicate that 20 mg/day rimonabant, in combination with diet and exercise, can produce a clinically meaningful reduction in bodyweight and improve HbA_{1c} and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulphonylureas.**

Introduction

Type 2 diabetes frequently co-exists with a cluster of other cardiovascular and metabolic risk factors including abdominal obesity, low HDL-cholesterol concentrations, high triglyceride concentrations, and raised blood pressure,[1] and is considered to be a cardiovascular disease risk equivalent.[2,3] A recent population-based retrospective cohort study showed that diabetes confers an equivalent cardiovascular risk to ageing 15 years in people aged 40 years or older.[4] The treatment of multiple cardiovascular and metabolic risk factors is central to the management of type 2 diabetes.[5]

Being overweight or obese—in particular, abdominally obese—increases the risk of type 2 diabetes and cardiovascular disease,[6,7] yet those with diabetes often have more difficulty in losing weight[8] and experience weight gain associated with most antidiabetic medications.[5]

The endocannabinoid system, consisting of the cannabinoid type 1 (CB_1) receptor and endogenous lipid-derived ligands,[9] seems to modulate energy homoeostasis as well as glucose and lipid metabolism,[10–12] both through central orexigenic effects and peripheral metabolic effects in adipose tissue, liver, and skeletal muscle.[13–15] Patients with obesity or hyperglycaemia caused by type 2 diabetes exhibit higher concentrations of endocannabinoids in visceral fat or serum, respectively, than the corresponding controls.[16]

In non-diabetic overweight or obese patients, 20 mg daily of the selective CB_1 receptor blocker rimonabant has been shown to produce substantial weight loss and waist circumference reduction (a key marker of intra-abdominal adiposity), and improvements in multiple cardiovascular and metabolic risk factors.[17,18] These data were further confirmed in overweight or obese patients with untreated dyslipidaemia.[19] Part of these metabolic improvements could be attributed to a moderate, but significant, increase in plasma adiponectin levels.[19]

This multicentre randomised controlled trial was designed to assess the efficacy and safety of rimonabant in combination with a mild hypocaloric diet and advice for increased physical activity in overweight or obese patients with type 2 diabetes who were already on metformin or sulphonylurea monotherapy.

Methods

Patients

This randomised, double-blind, placebo-controlled study was done in 159 centres in 11 countries (in Europe, North America, and South America) between October, 2001, and May, 2004. Patients aged 18–70 years with type 2

diabetes who had been treated with metformin or sulphonylurea monotherapy for at least 6 months (stable dose for at least 3 months), but who remained inadequately controlled, were recruited. Inclusion criteria were body-mass index of 27–40 kg/m², a haemoglobin A_{1c} (HbA_{1c}) level of 6·5–10·0%, and a fasting glucose concentration of 5·55–15·04 mmol/L. Exclusion criteria were unstable bodyweight (defined as more than 5 kg variation within the past 3 months), any clinically significant disorder (including severe microvascular or macrovascular complications of diabetes), systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 95 mm Hg, pregnancy or lactation, recent or planned changes in smoking status, use of anti-obesity drugs within the past 3 months, or use of any medication known to affect bodyweight (eg, anti–depressants). Written informed consent was obtained from all patients.

The protocol was approved by the Institutional Review Board/Ethics Committee for each centre. The study was done in full compliance with the Declaration of Helsinki, with an independent, unblinded data safety monitoring board.[17–19]

Procedures

The protocol has been described previously.[17–19] A 2-week screening period preceded a 4-week, placebo run-in period, followed by randomisation to double-blind treatment. A randomisation code list, with a block size of three, was generated centrally by the sponsor. Treatments were allocated to patients with an interactive voice response system in accordance with the predefined randomisation list (1/1/1 ratio for placebo, 5 mg/day rimonabant, or 20 mg/day rimonabant, respectively). The interactive voice response system ensured that the randomisation of treatment was balanced within all centres and was stratified on the basis of bodyweight loss (≤2 kg or >2 kg) during the run-in period and class of antidiabetic medication. All patients were put on a mild hypocalorific diet and were advised on increased physical activity during the run-in period and until the end of the study.

Standardised assessments of bodyweight, waist circumference, and vital signs were done at screening, twice during the run-in period, at baseline (randomisation), and post-randomisation at week 2, week 4, and monthly thereafter for 1 year. Glycaemic and lipid variables were measured at screening, baseline, week 12, 24, and 36, and at 1 year. Insulin resistance was calculated by use of the homoeostasis model assessment (HOMA-IR).[20] The diagnosis of metabolic syndrome was assessed in accordance with National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) criteria.[2]

The primary endpoint was weight change from baseline at the last observation carried forward (LOCF). Secondary endpoints included changes in HbA_{1c}, HDL cholesterol, triglyceride, fasting glucose, fasting insulin, high-sensitivity C-reactive protein (hsCRP), and leptin concentrations, prevalence of metabolic syndrome,[2] waist circumference, and blood pressure. Measurements of HbA_{1c}, glucose, insulin, total cholesterol, LDL and HDL cholesterol, triglyceride, leptin, and hsCRP were done at central laboratories (ICON Laboratories, Farmingdale, NY, USA and Dublin, Ireland), together with laboratory safety measurements in accordance with standard procedures.[17–19] HbA_{1c} was measured by ion exchange high-pressure liquid chromatography (Bio-Rad variant, Bio-Rad Laboratories, Hercules, CA, USA) with Diabetes Control and Complications Trial reference values.

The SF36 health survey questionnaire[21] and a patient's satisfaction scale were included in the study as exploratory secondary parameters. Patients completed the obesity-specific Impact of Weight on Quality of Life (IWQoL-Lite) exploratory secondary questionnaire at baseline and every 3 months for 1 year.[22,23] Food behaviour was also assessed by a Visual Analog Scale.[24]

Safety assessment was done regularly by an independent data safety and monitoring board and included standard adverse event reporting, vital signs, pulse-rate-corrected QT interval, and the Hospital Anxiety and Depression (HAD) scale.[25]

Statistical analysis

The sample size was calculated on the basis of the assumption that the SD of weight change at year 1 would be 10 kg. Thus 990 randomised patients (330 patients in every group) would provide 95% confidence to detect a 3 kg difference between both doses of rimonabant and placebo after 1 year. An α level of 0·025 was chosen to ensure an overall type error rate of 0·05 according to a modified Bonferroni procedure.

Analyses were done on a modified intention-to-treat basis. The modified intention-to-treat population consisted of all randomised patients who were exposed to at least one dose of study drug and had at least one post-baseline assessment and, when appropriate, a baseline assessment.

The primary endpoint was analysed with analysis of variance with the modified Bonferroni procedure (Hochberg) to adjust for multiple doses.[26] The three-way analysis of variance (ANOVA) model included terms for treatment and two randomisation strata (weight loss of ≤2 kg or >2 kg during the run-in period and antidiabetic therapy with metformin or sulphonylurea); both doses of rimonabant were compared with placebo. As an assessment of sensitivity, a post-hoc repeated measures approach was done for changes in weight from baseline, because this analysis includes all measurements gathered over time during the study, and thus might provide a better assessment in the presence of missing data.[27]

The repeated measures model included a number of fixed effects (randomisation strata, treatment, number of days from randomisation, and treatment-by-day

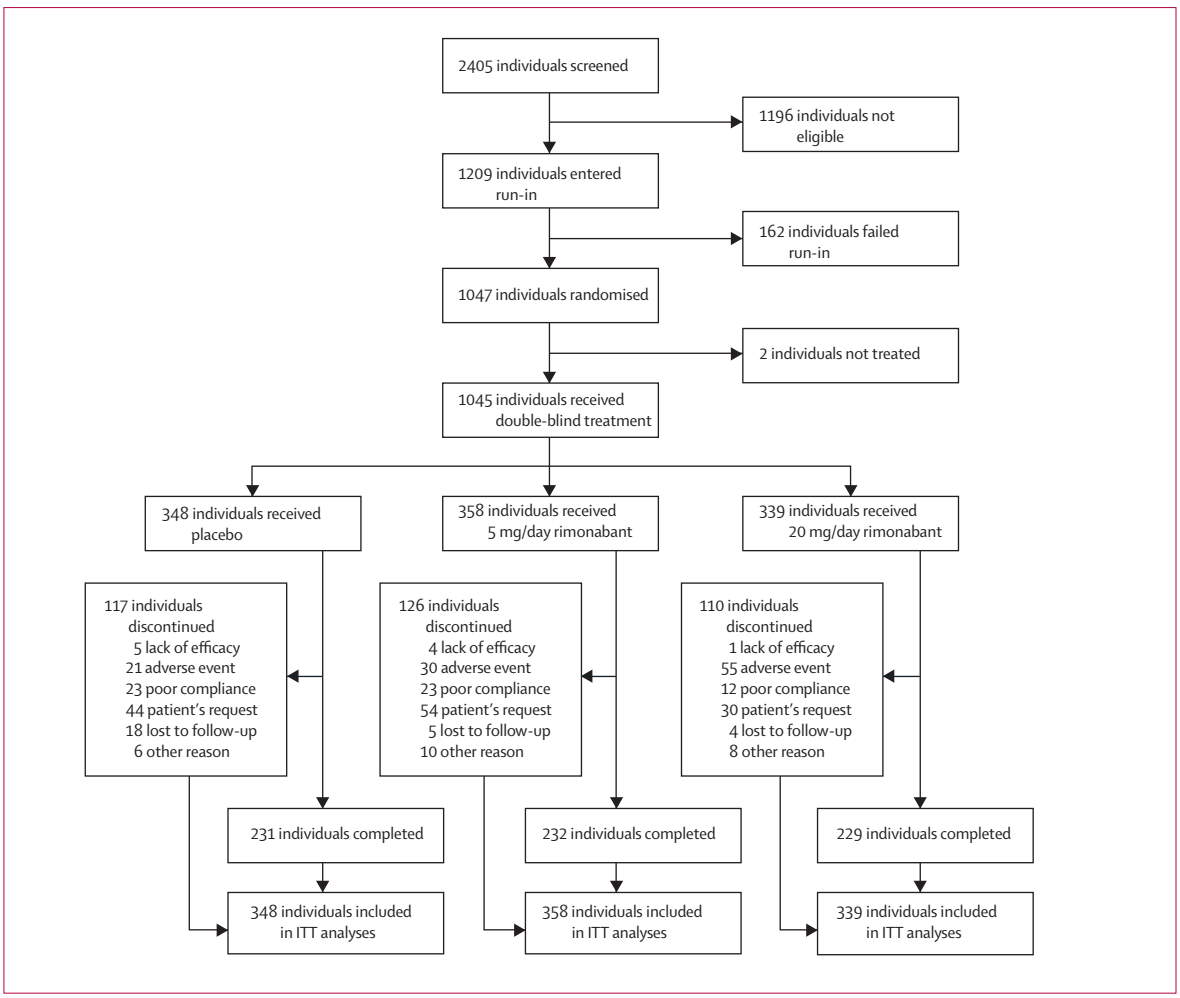


Figure 1: **Trial profile**
ITT=intention-to-treat.

interaction) and a random effect (the patient). Additionally, as another assessment of sensitivity, a more conservative method than LOCF for handling missing data was used. For dropouts with post-baseline efficacy, the last value was set to the baseline value—ie, baseline observation carried forward (BOCF)—and the change from baseline was set to zero.[28] Similar models, excluding randomisation strata, were applied to the secondary efficacy parameters.

Patients were classified as having a response of a 5% or 10% weight loss if they had a reduction in bodyweight from baseline at the LOCF of at least 5% or 10%. The incidences of patients who had a weight loss of 5% and 10% and of those with metabolic syndrome at LOCF were analysed with logistic regression models. The models for patients who had weight losses of 5% and 10% included terms for treatment and randomisation strata, and the model for the metabolic syndrome included terms for treatment and the status of the metabolic syndrome at baseline.

The effect of rimonabant independent of weight loss was tested with analysis of covariance (ANCOVA) with weight loss (change in weight from baseline to 1 year) as a covariate.[28] The statistical model for the weight-adjusted treatment effect is as follows: $Y=a+\beta T+\gamma W+e$ (ANCOVA model, weight adjusted) where Y is the efficacy variable, T is the treatment indicator, and W is weight loss. The weight-independent portion of the total treatment effect was calculated as the ratio of the weight-adjusted treatment effect, β, to the treatment effect in the overall unadjusted ANOVA model, β_1, determined from the ANOVA model: $Y=a+\beta_1 T+e_1$.[29] This ratio indicates the proportion of the total effect size that cannot be explained by weight loss.

All statistical tests were two-sided; all p values presented are unadjusted. Analyses were done with SAS software, version 8.2.

This trial is registered at ClinicalTrials.gov, number NCT00029848.

Role of the funding source

The sponsor participated in discussions regarding study design and protocol development and provided logistical support during the trial. Data were gathered by the sponsor and were assessed jointly by the authors and the sponsor. Data were interpreted and the manuscript written by the authors, with editorial support provided by the sponsor. The corresponding author had full access to all the data and takes responsibility for the integrity of that data and the accuracy of the data analysis. The corresponding author had final responsibility for the decision to submit for publication.

Results

513 men and 532 women were randomised to double-blind treatment. 692 patients (66·2%) completed the 1-year follow-up (figure 1). Two randomised patients were not exposed to treatment and 11 randomised patients were excluded from the analysis of weight (two for non-exposure and nine for missing post-baseline weight assessment). Baseline characteristics were much the same in the three groups (table 1), except smoking, which was slightly lower in the 20 mg/day rimonabant group (p=0·02), and fasting triglyceride concentrations, which were slightly higher in the 20 mg/day rimonabant group (p=0·03) At screening, mean weight was 96·3 kg (SD 14·7), mean waist circumference 109 cm (10·8), mean HbA_{1c} 7·3% (0·9), mean fasting plasma glucose concentration of 8·3 mmol/L (2·1), and mean prevalence of metabolic syndrome was 79%. Mean reductions in weight (–1·5 kg [1·8]), waist circumference (–1·4 cm [3·3]), HbA_{1c} (–0·24% [0·54]), fasting plasma glucose concentration (–0·52 mmol/L [1·87]), fasting plasma insulin concentration (–1·1 µIU/mL [10·5]), triglyceride concentration (–1·3% [35·3]), HDL-cholesterol concentration (–1·9% [11·5]), and systolic blood pressure (–2·1 mm Hg [11·7]) were seen after the placebo run-in. 99·4% (338 of 340), 98·9% (349 of 353), and 99·1% (336 of 339) of the randomised and exposed patients for whom compliance data were available in the placebo, 5 mg/day, and 20 mg/day groups, respectively, achieved compliance of 80% or more with the study medication.

Weight loss was significantly greater with both doses of rimonabant than with placebo, independent of age and sex (p=0·01 for 5 mg *vs* placebo, p<0·0001 for 20 mg *vs* placebo; table 2 and figure 2). The placebo-corrected weight loss after 1 year of treatment with 20 mg/day rimonabant was 3·9 kg (SD 0·3); placebo-subtracted losses were 4·3 kg (0·4) in patients treated with metformin and 3·1 kg (0·5) in those treated with sulfonylurea after 1 year of 20 mg/day rimonabant (p<0·0001 for both). The number of patients achieving weight loss of 5% or more and 10% or more at the last follow-up visit was also significantly greater in both groups receiving rimonabant than in the placebo group (≥5% loss: p=0·02 for 5 mg and p<0·0001 for 20 mg; ≥10% loss: p=0·01 for 5 mg and p<0·0001 for 20 mg;

	Placebo group (n=348)	5 mg/day rimonabant group (n=358)	20 mg/day rimonabant group (n=339)
Demographics at screening*			
Age (years)	54·8 (8·6)	55·9 (8·6)	56·0 (8·5)
Sex (% male)	159 (46%)	186 (52%)	168 (50%)
Race			
White (%)	308 (89%)	315 (88%)	302 (89%)
Black (%)	18 (5%)	20 (6%)	19 (6%)
Weight (kg)	97·5 (15·1)	98·7 (15·1)	97·1 (14·4)
Waist (cm)			
Male	114·7 (10·6)	113·6 (10·6)	112·9 (10·0)
Female	106·5 (10·1)	107·1 (10·2)	107·0 (10·2)
Body-mass index (kg/m²)	34·2 (3·6)	34·4 (3·6)	34·1 (3·6)
HbA_{1c} (%)	7·5% (0·9)	7·5% (0·8)	7·5% (0·8)
Current smokers (%)	51 (15%)	43 (12%)	30 (9%)
Hypertension (%)†	206 (59%)	218 (61%)	216 (64%)
Dyslipidaemia (%)‡	186 (53%)	202 (56%)	193 (57%)
Antidiabetic treatment			
Metformin	230 (66%)	230 (64%)	218 (64%)
Sulphonylureas	118 (34%)	128 (36%)	121 (36%)
Efficacy at baseline			
Weight (kg)	96·0 (15·1)	97·2 (14·8)	95·7 (14·2)
Waist (cm)			
Male	113·7 (11·0)	112·0 (10·5)	111·3 (9·6)
Female	105·3 (10·6)	106·4 (10·1)	106·0 (9·9)
HbA_{1c} (%)	7·2% (0·9)	7·3% (0·8)	7·3% (0·8)
Fasting glucose (mmol/L)	8·2 (2·2)	8·2 (1·8)	8·5 (2·2)
Fasting insulin (µIU/mL)	16·0 (13·3)	14·9 (9·3)	15·5 (11·3)
HOMA-IR	5·8 (7·3)	5·3 (3·5)	5·9 (5·0)
Triglycerides (mmol/L)	1·93 (1·05)	1·95 (1·01)	2·12 (1·29)
HDL cholesterol (mmol/L)			
Men	1·06 (0·23)	1·06 (0·22)	1·08 (0·22)
Women	1·26 (0·28)	1·28 (0·28)	1·24 (0·28)
LDL cholesterol (mmol/L)	2·99 (0·80)	2·98 (0·80)	2·99 (0·82)
Total cholesterol (mmol/L)	5·00 (0·96)	4·99 (0·97)	5·06 (0·97)
Total cholesterol/HDL cholesterol	4·48 (1·17)	4·46 (1·20)	4·52 (1·19)
Non-HDL cholesterol (mmol/L)	3·83 (0·92)	3·83 (0·2)	3·89 (0·95)
Metabolic syndrome§	271 (79%)	276 (80%)	267 (79%)
Supine systolic blood pressure (mm Hg)	128·7 (13·1)	130·9 (13·4)	130·3 (12·5)
Supine diastolic blood pressure (mm Hg)	78·8 (7·8)	79·0 (7·9)	79·0 (7·8)
hsCRP (mg/L)	6·3 (8·1)	5·9 (7·3)	5·4 (6·5)
Leptin (ng/mL)	16 (8·7)	16 (9·3)	16 (9·1)
Safety at baseline			
Heart rate (bpm)	67·0 (10·3)	64·8 (9·8)	68·5 (10·6)
QTcF (ms)¶	406·0 (19·1)	406·0 (21·1)	407·4 (18·1)
HAD/depression‖	3·1 (2·8)	2·8 (2·6)	3·1 (2·9)
HAD/anxiety‖	5·2 (3·4)	4·9 (3·2)	5·1 (3·6)

Data are number (%) or mean (SD). *Screening data split into treatment groups retrospectively after randomisation. †Defined as systolic blood pressure ≥130 mm Hg or supine diastolic blood pressure ≥85 mm Hg, or both; overall 93% of patients with hypertension were treated. ‡Defined for men as LDL-cholesterol concentration ≥3·36 mmol/L, or HDL-cholesterol concentration <1·03 mmol/L for men and <1·3 mmol/L for women, or triglyceride concentration ≥1·69 mmol/L; overall 65% of patients with dyslipidaemia were treated. §Patients had metabolic syndrome as detected according to NCEP-ATP III.[2] Data on metabolic syndrome at baseline available for 342, 347, and 337 patients in the placebo, 5 mg, and 20 mg groups, respectively. ¶QT interval corrected for heart rate. ‖HAD=Hospital Anxiety and Depression. The HAD scale consists of 14 items measuring the level of anxiety and depression in two separate subscales. Scale scores range from 0 (no symptoms) to 21 (maximum distress) for both depression and anxiety and is interpreted with the following cut points: 0–7=normal, 8–10=mild disturbance (probable case), ≥11=moderate to mood disturbance (definite case).

Table 1: **Characteristics of participants**

	Placebo	5 mg/day rimonabant	20 mg/day rimonabant	p value (5 mg *vs* placebo)	p value (20 mg *vs* placebo)
Weight					
Number of patients with data at last visit	345	355	336		
Change from baseline (kg)	−1·4 (3·6)	−2·3 (4·2)	−5·3 (5·2)	0·01	<0·0001
≥5% weight loss	50 (14·5%)	77 (21·7%)	166 (49·4%)	0·02	<0·0001
≥10% weight loss	7 (2·0%)	22 (6·2%)	55 (16·4%)	0·01	<0·0001
Waist circumference					
Number of patients with data at last visit	344	355	336		
Change from baseline (cm)	−1·9 (5·5)	−2·9 (5·6)	−5·2 (6·1)	0·02	<0·0001
HbA_{1c}					
Number of patients with data at last visit	317	330	315		
Change from baseline (%)	0·1% (1·0)	−0·1% (1·0)	−0·6% (0·8)	0·03	<0·0001
Patients that achieved HbA_{1c} <6·5%	66 (21%)	78 (24%)	135 (43%)	0·39	<0·0001
Patients that achieved HbA_{1c} <7%	151 (48%)	168 (51%)	214 (68%)	0·40	<0·0001
Change from baseline in patients taking metformin* (%)	0·1% (1·0)	−0·1% (1·1)	−0·6% (0·8)	0·19	<0·0001
Change from baseline in patients taking sulphonylurea† (%)	0·1% (1·1)	−0·1% (0·9)	−0·5% (0·8)	0·07	<0·0001
Fasting glucose concentration					
Number of patients with data at last visit	317	331	317		
Change from baseline (mmol/L)	0·33 (2·32)	0·30 (2·06)	−0·64 (1·96)	0·86	<0·0001
Fasting insulin					
Number of patients with data at last visit	314	328	311		
Change from baseline (μIU/mL)	0·4 (14·8)	0·7 (9·0)	−0·7 (9·9)	0·76	0·25
HOMA-IR					
Number of patients with data at last visit	308	319	309		
Change from baseline	0·6 (8·9)	0·6 (4·2)	−0·5 (5·7)	0·97	0·03
HDL cholesterol‡					
Number of patients with data at last visit	314	331	318		
Change from baseline (mmol/L)	0·07 (0·15)	0·11 (0·19)	0·17 (0·20)	0·02	<0·0001
Change from baseline (%)	7·1% (13·5)	9·2% (15·8)	15·4% (17·4)	0·08	<0·0001
Triglycerides‡					
Number of patients with data at last visit	314	330	317		
Change from baseline (mmol/L)	0·04 (0·87)	−0·01 (0·79)	−0·35 (1·28)	0·50	<0·0001
Change from baseline (%)	7·3% (43·0)	1·3% (35·1)	−9·1% (44·3)	0·07	<0·0001
Total cholesterol/HDL cholesterol ratio					
Number of patients with data at last visit	314	330	317		
Change from baseline	−0·16 (0·79)	−0·23 (0·80)	−0·51 (0·82)	0·27	<0·0001
Change in non-HDL cholesterol‡					
Number of patients with data at last visit	314	330	317		
Change from baseline (mmol/L)	0·02 (0·85)	0·00 (0·75)	−0·13 (0·80)	0·70	0·02
Change from baseline (%)	2·5% (22·5)	2·0% (21·1)	−1·8% (21·0)	0·75	0·01
Total cholesterol‡					
Number of patients with data at last visit	314	331	317		
Change from baseline (mmol/L)	0·10 (0·88)	0·11 (0·76)	0·04 (0·82)	0·90	0·36
Change from baseline (%)	3·3% (17·7)	3·3% (16·2)	2·0% (16·5)	0·98	0·32
LDL cholesterol‡					
Number of patients with data at last visit	314	331	317		
Change from baseline (mmol/L)	0·13 (0·76)	0·13 (0·66)	0·09 (0·79)	0·99	0·52
Change from baseline (%)	7·2% (26·3)	7·5% (26·8)	6·9% (34·5)	0·89	0·90
Metabolic syndrome					
Number of patients with data at last visit	316	331	318		
Improvement at 1 year	44/251 (18%)	57/260 (22%)	66/252 (26%)	0·21	0·02
Development at 1 year	25/65 (38%)	21/71 (30%)	18/66 (27%)	0·28	0·17

(Continues on next page)

(Continued from previous page)

Supine systolic blood pressure					
Number of patients with data at last visit	345	355	336		
Change from baseline (mm Hg)	1·6 (13·2)	−0·4 (12·9)	−0·8 (12·8)	0·04	0·02
Supine diastolic blood pressure					
Number of patients with data at last visit	345	355	336		
Change from baseline (mm Hg)	−0·7 (8·4)	−0·4 (8·5)	−1·9 (8·2)	0·70	0·06
hsCRP					
Number of patients with data at last visit	308	323	313		
Change from baseline (mg/L)	−0·0 (10·0)	−0·5 (5·8)	−1·4 (5·2)	0·48	0·02
Leptin					
Number of patients with data at last visit	290	308	294		
Change from baseline (ng/mL)	3·1 (7·5)	1·9 (6·1)	−0·3 (6·0)	0·03	<0·0001

Data are mean (SD) or n/N (%), unless otherwise indicated. HOMA-IR=Homoeostasis Model of Assessment of insulin resistance. *n=211, n=209, and n=204 in the placebo, 5 mg/day, and 20 mg/day rimonabant groups, respectively, at the end of study. †n=106, n=121, n=111 in the placebo, 5 mg/day, and 20 mg/day rimonabant groups, respectively, at the end of study. ‡Analyses of cholesterol (total, LDL, HDL, and non-HDL) and triglycerides were done on percent changes from baseline.

Table 2: **Changes in weight and risk factors**

table 2). Waist circumference was significantly lower with both doses of rimonabant than with placebo (p=0·02 for 5 mg, p<0·0001 for 20 mg; table 2 and figure 2B).

HbA_{1c} levels were lower with both doses of rimonabant than with placebo (p=0·03 for 5 mg and p<0·0001 for 20 mg; table 2 and figure 3A and B) with a sustained decline in the 20 mg/day rimonabant group (figure 3A). Treatment with metformin or sulphonylurea did not affect HbA_{1c} levels (table 2). More patients in the 20 mg/day rimonabant group reached an HbA_{1c} target of less than 6·5%[30] and less than 7%[31] than did those in the placebo group (p<0·0001 for both target levels; table 2). The observed effects of 20 mg/day rimonabant on HbA_{1c} were about twice that attributable to concurrent weight loss alone after adjustment with ANCOVA (figure 3C). For example, of the observed placebo-subtracted 0·7% reduction in HbA_{1c} with 20 mg/day rimonabant, 0·4% (SD 0·1) remained after weight-loss adjustment, equivalent to 57% (10) of the overall response (p<0·0001). In the 20 mg/day rimonabant group more patients needed downward adjustment of their antidiabetic medication than did those in the placebo group (table 3).

Improvements in fasting glucose concentrations and HOMA-IR were greater in the 20 mg/day rimonabant group than in the placebo group (p<0·0001 and p=0·03, respectively; table 2). HDL cholesterol, triglyceride, and non-HDL-cholesterol concentrations also improved more with 20 mg/day rimonabant than with placebo (p<0·0001 for all; table 2 and figure 2C and D). The residual effect on HDL-cholesterol concentration of 20 mg/day rimonabant was 57% (14) of the observed effect after adjustment for weight loss (p<0·0001). The residual effect on triglyceride concentration after adjustment for weight loss was 36% (20) of the observed effect, which was not significant (p=0·08). The persisting prevalence of the metabolic syndrome was lower in the 20 mg/day rimonabant group than in the placebo group at 1 year (p=0·02; table 2). Supine systolic blood pressure was lower in both rimonabant groups than it was in the placebo group (p=0·04 for 5 mg, p=0·02 for 20 mg; table 2). However, the residual effect on supine systolic blood pressure after adjustment for weight loss was 48% (42) of the observed effect, which was not significant (p=0·30). The prevalence of hypertension in the 20 mg/day rimonabant group was much the same as that in the placebo group and it did not differ between baseline and 1 year of treatment (54·8% *vs* 53·9%, respectively, in the 20 mg/day group). The decrease in hsCRP levels was greater in the 20 mg/day rimonabant group than it was in the placebo group (p=0·02; table 2). Change in fibrinogen concentrations were much the same in all three groups (data not shown). Leptin levels—a marker of fat mass—were lower in the 20 mg/day rimonabant group than they were in the placebo group (p<0·0001; table 2).

Improvements were seen for all food behaviour parameters in the 20 mg/day rimonabant group at 1 year. Patients in the 20 mg/day rimonabant group reported less appetite (p<0·0001), easier to follow the diet (p<0·0001), less desire for high fat foods (p=0·0003), and less desire for sweets (p=0·04) than did those in the placebo group (data not shown). A number of exploratory secondary parameters were investigated as per protocol. A greater improvement in physical functioning (as assessed by SF36; p=0·012; data not shown) and a greater impairment in mental health score (p=0·022) were recorded at 1 year in the 20 mg/day rimonabant group than in the placebo group (data not shown). Furthermore, more patients on 20 mg/day rimonabant reported being "very" or "exceptionally" satisfied at 1 year than did patients on placebo (p=0·001), as assessed by a patient's satisfaction scale (data not shown). Health-related quality of life was specifically

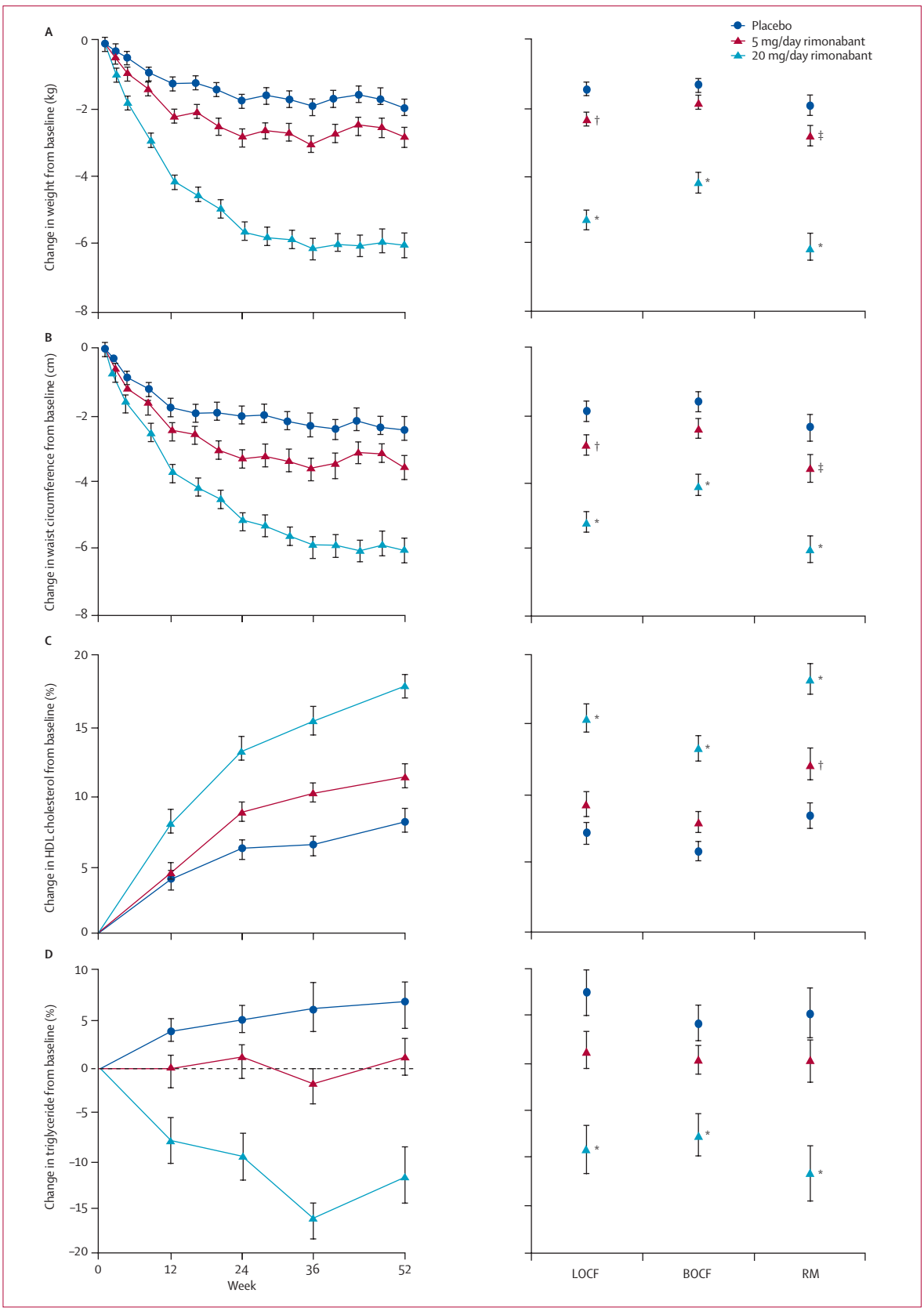


***Figure 2*: Changes in weight, waist, HDL cholesterol, and triglycerides**

(A) Mean (SE) change from baseline in bodyweight over 1 year; last observation carried forward (LOCF), baseline observation carried forward (BOCF), and repeated measures (RM). *p<0·001, †p=0·01, ‡p=0·03 *vs* placebo. (B) Mean (SE) change from baseline in waist circumference over 1 year; LOCF, BOCF, and RM. *p<0·001, †p=0·02, ‡p=0·03 *vs* placebo. (C) Mean (SE) percentage change from baseline in HDL-cholesterol concentration over 1 year; LOCF, BOCF, and RM. *p<0·001, †p=0·05 *vs* placebo. (D) Mean (SE) percentage change from baseline in triglyceride levels over 1 year; LOCF, BOCF, and RM. *p<0·001 *vs* placebo.

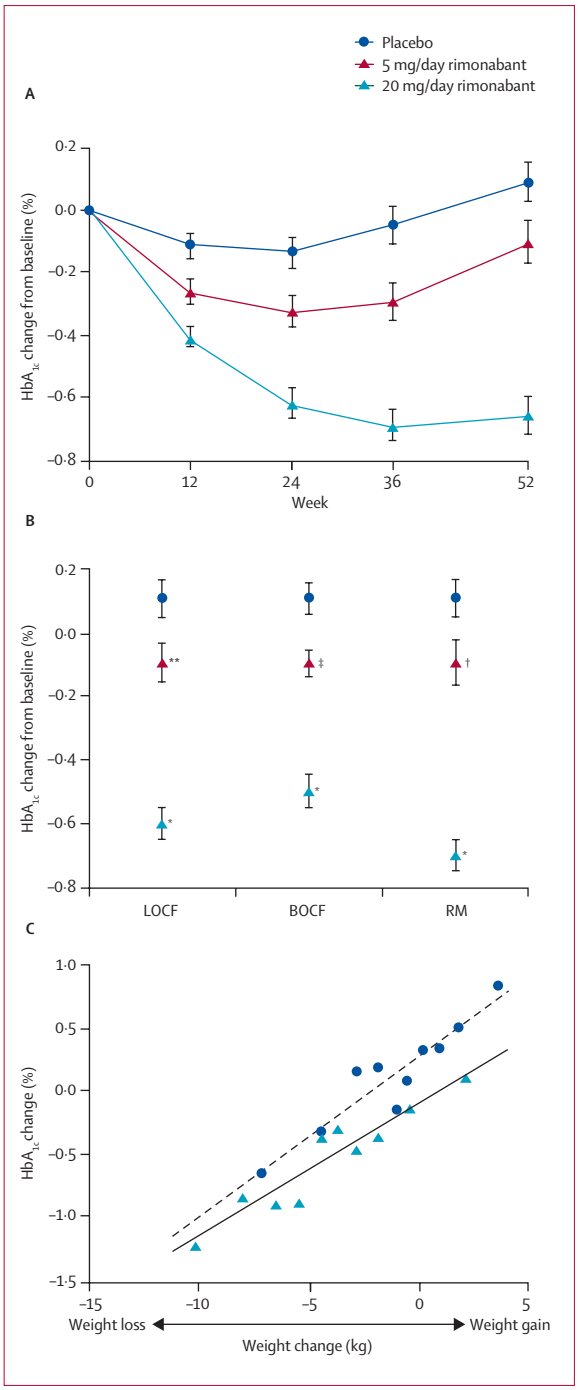


Figure 3: **Changes in HbA_{1c} levels**
(A) Mean (SE) change from baseline in HbA_{1c} levels over 1 year. (B) Mean (SE) change from baseline in HbA_{1c} levels: last observation carried forward (LOCF), baseline observation carried forward (BOCF), and repeated measures (RM). *p<0·0001, †p=0·03, ‡p=0·04, §p=0·05 *vs* placebo. (C) Linear regression analysis between HbA_{1c} changes and bodyweight changes, excluding patients with extreme weight loss (≥11·2 kg), in patients receiving placebo or 20 mg/day rimonabant. The weight change data from lowest to highest was divided into ten groups with about equal sample size (deciles) and within each decile the mean weight change and the mean change in HbA_{1c} was calculated. The pairs of mean changes (weight, HbA_{1c}) were plotted along with the regression line to illustrate the relation between weight loss and HbA_{1c}.

assessed with IWQoL-Lite. A greater improvement at 1 year in the physical function (p=0·002) and self-esteem domains (p=0·004) and in the total IWQoL-Lite score (p=0·006) was noted in the 20 mg/day rimonabant group than in the placebo group (data not shown).

A slightly greater proportion of patients in the rimonabant treatment groups experienced adverse events than did those in the placebo group (table 4). The most common adverse events, occurring in 5% or more rimonabant-treated patients, were nausea, diarrhoea, vomiting, dizziness, hypoglycaemia, fatigue, and anxiety (table 4); these were generally mild or moderate, transient and self-limited, and seen early in the treatment period. In the 20 mg/day rimonabant group, hypoglycaemia was reported more frequently in diabetic patients treated with sulphonylureas than in those given metformin, but only one case led to treatment discontinuation.

Although overall discontinuation rates were much the same in all groups, discontinuations due to adverse events were more frequent in the 20 mg/day and 5 mg/day rimonabant groups than they were in the placebo group (table 4). Dropouts due to adverse events in the 20 mg/day group were much the same in patients who lost weight (−5 kg or more) as in those who gained weight (≥0 kg)—10·6% (16 of 151 patients) and 12·8% (5 of 39 patients), respectively. The most common adverse events that led to premature study discontinuation in the 20 mg/day rimonabant group were depressed mood disorders, nausea, and dizziness (table 4). However, no serious adverse events linked to psychiatric disorders were recorded in either rimonabant group.

Cardiovascular safety endpoint measures and HAD depression and anxiety subscores were much the same across the three treatment arms at baseline and at 1 year (table 1 and table 4). Although there was a trend towards slight increases in both HAD scores in the 20 mg/day rimonabant group compared with the placebo group, the observed increases should be considered to be marginal.

Discussion

The main finding of the RIO-Diabetes trial is that 20 mg/day rimonabant for 1 year significantly reduced weight, waist circumference, and HbA_{1c} levels and improved a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylurea. These results extend previous findings in non-diabetic overweight or obese patients to those with type 2 diabetes.[17–19] Patients with type 2 diabetes are characterised by resistance to weight loss,[8] overactivity of the endocannabinoid system,[16] and increased cardiovascular risk,[2,3] with obesity being deemed to be an additional and independent risk factor.[32]

Treatment with 20 mg/day rimonabant enabled a greater number of patients on monotherapy with metformin or

	Placebo (n=345)	5 mg/day rimonabant (n=355)*	20 mg/day rimonabant (n=336)†
No change	268 (77·7%)	279 (78·6%)	255 (75·9%)
Increase	44 (12·8%)	49 (13·8%)	38 (11·3%)
Decrease	26 (7·5%)	22 (6·2%)	40 (11·9%)
Another drug added due to insufficient efficacy	7 (2·0%)	3 (0·8%)	0 (0%)
Another drug added due to other reasons	0 (0%)	2 (0·6%)	3 (0·9%)

Data are number (%). *p=0·42 for all categories *vs* placebo. †p=0·005 for all categories *vs* placebo.

Table 3: **Distribution of dose changes in antidiabetic medications**

sulphonylurea whose baseline HbA_{1c} levels were close to the American Diabetes Association recommended level (7%) to attain such a target.[31] The placebo-corrected reduction in HbA_{1c} levels of 0·7% seen with 20 mg/day rimonabant is clinically relevant, since every 1% reduction in HbA_{1c} has been shown to be associated with a reduction in risk of 21% for any endpoint related to diabetes.[33] For the purpose of comparison, in metformin-treated diabetic patients, treatment with twice-daily subcutaneous injection of 10 µg exenatide induced a 0·86% placebo-subtracted reduction in HbA_{1c} after 30 weeks, a decrease that is close to that recorded with 20 mg/day rimonabant with baseline HbA_{1c} levels above 8%.[34]

	Placebo (n=348)	5 mg/day rimonabant (n=358)	20 mg/day rimonabant (n=339)
Safety data at 1 year			
Overall dropout rate	117 (34%)	126 (35%)	110 (32%)
Patients with any adverse event	276 (79%)	293 (82%)	288 (85%)
Patients with any serious adverse event*	15 (4%)	27 (8%)	27 (8%)
Discontinuations due to adverse events	19 (5%)	28 (8%)	51 (15%)
Adverse events that led to study discontinuation†			
Psychiatric disorders			
Depressed mood disorders‡	3 (0·9%)	0	11 (3%)
Anxiety	0	0	2 (0·6%)
Aggression	0	2 (0·6%)	0
Nervous system disorders			
Headache	1 (0·3%)	1 (0·3%)	2 (0·6%)
Dizziness	0	0	3 (0·9%)
Paraesthesia	0	0	2 (0·6%)
Gastrointestinal disorders			
Nausea	1 (0·3%)	0	5 (1·5%)
Vomiting	0	0	2 (0·6%)
General disorders			
Chest pain	0	0	2 (0·6%)
Asthenia/fatigue	0	2 (0·6%)	1 (0·3%)
Adverse events with an incidence of ≥5% in any group			
Nausea	20 (6%)	22 (6%)	41 (12%)
Nasopharyngitis	74 (21%)	59 (16%)	41 (12%)
Dizziness	17 (5%)	11 (3%)	31 (9%)
Arthralgia	28 (8%)	35 (10%)	30 (9%)
Headache	32 (9%)	29 (8%)	28 (8%)
Diarrhoea	23 (7%)	22 (6%)	25 (7%)
Back pain	24 (7%)	22 (6%)	24 (7%)
Upper respiratory tract infection	33 (9%)	28 (8%)	23 (7%)
Vomiting	8 (2%)	14 (4%)	20 (6%)
Hypoglycaemia	6 (2%)	5 (1%)	18 (5%)
Fatigue	13 (4%)	19 (5%)	18 (5%)
Anxiety	9 (3%)	4 (1%)	17 (5%)

(Continues on next page)

(Continued from previous page)

Safety endpoints			
Heart rate (bpm)‡			
Number of patients with data at last visit	314	332	314
Year 1	67·8 (10·8)	69·3 (10·1)	69·5 (11·4)
Change from baseline	0·8 (8·8)	0·9 (8·7)	1·0 (10·2)
QTcF (ms)‡			
Number of patients with data at last visit	313	331	314
Last recorded value	403·9 (20·1)	404·4 (19·8)	407·1 (19·4)
Change from baseline	−2·1 (16·6)	−1·6 (16·3)	−0·3 (15·4)
HAD/depression‡			
Number of patients with data at last visit	279	286	262
Last recorded value	2·9 (3·0)	2·7 (2·8)	3·3 (3·3)
Change from baseline	−0·2 (2·6)	−0·1 (2·3)	0·3 (2·9)
HAD/anxiety‡			
Number of patients with data at last visit	279	285	262
Last recorded value	4·9 (3·6)	4·7 (3·6)	5·5 (4·0)
Change from baseline	−0·3 (3·2)	−0·1 (2·7)	0·4 (3·4)

Data are number (%) or mean (SD), unless otherwise indicated.*There was one death during the placebo run-in period (cardiac arrest) and four deaths during the double-blind treatment period. One patient in the 5 mg/day rimonabant group died of septic shock 6 months after starting the study treatment, while in the 20 mg/day rimonabant group, one patient was a passenger in a traffic accident (more than 6 months after the start of study treatment) and two metformin-treated patients with multiple risk factors died of a cardiovascular disease (one death 2 months and the other 5 months after the start of study treatment). No causal relation to the study drug was suspected by the investigators for any death. In the overall RIO trial programme (n=6625; four studies), deaths were equally distributed across groups (four in the placebo group, three in the 5 mg/day rimonabant group, and four in the 20 mg/day rimonabant group). †According to MedDRA, in at least two patients in any rimonabant group and in main system organ class (≥1%). One patient can report several events. ‡Depressed mood disorders corresponded to the MedDRA HLGT term "Depressed mood disorders and disturbances" and consist of depression, major depression, depressed mood, and depressive symptoms.

Table 4: **Safety data at 1 year and adverse events in randomised and exposed patients**

Improved glycaemic control has an important beneficial effect on the risk of microvascular and macrovascular complications related to diabetes.[33] Nevertheless, in recent years considerable emphasis has been placed on aggressive management of multiple cardiovascular and metabolic risk factors in type 2 diabetes patients.[35,36] 20 mg/day rimonabant improved atherogenic dyslipidaemia and diminished systolic blood pressure in diabetic patients, and also reduced the prevalence of metabolic syndrome,[37] as already reported in overweight dyslipidaemic non-diabetic patients.[19] Compared with placebo, 20 mg/day rimonabant also reduced hsCRP levels, an inflammatory biomarker considered to be a moderate predictor of cardiovascular disease.[38]

57% of placebo-subtracted effects of 20 mg/day rimonabant on HDL-cholesterol concentrations and HbA_{1c} levels were independent of weight loss, consistent with the direct peripheral metabolic effects of the drug.[13,15,17,18,39] Rimonabant increases the secretion of adiponectin,[19] an adipokine whose plasma concentrations correlates positively with insulin sensitivity, and levels of which are lower both in obese and type 2 diabetic patients than in lean healthy individuals.[40] Although low adiponectin levels have been deemed to be a predictor of cardiovascular disease, further studies are needed to confirm this association.[41] The blockade of CB_1 receptors might also inhibit hepatic fatty acid synthesis and hepatic lipid accumulation, which have also been implicated in insulin resistance and dyslipidaemia.[14]

Intentional weight loss in overweight or obese type 2 diabetes patients improves lipid profile, blood pressure, and diabetes control.[5] Weight loss has been shown to be associated with a reduced mortality risk in observational studies,[42] although such an association has not been recorded in randomised clinical trials yet. Although only moderate weight loss (5–10% of bodyweight) is required to improve glycaemic control, weight loss and maintenance of weight loss in patients with type 2 diabetes are generally more difficult than in non-diabetic individuals.[8,43] Furthermore, most antidiabetic medications (in particular sulphonylureas, thiazolidinediones, and insulin) produce concomitant weight gain.[5,31,44] In this study, a mean weight loss of 6·1 kg was noted in patients who completed the 1-year treatment with 20 mg/day rimonabant, much the same as that described in the Diabetes Prevention Program (DPP),[45] in which patients were treated with an intensive lifestyle intervention. However, lifestyle intervention in the DPP was highly demanding and applied to non-diabetic individuals, a population that has less difficulty in losing weight than diabetic patients.[8] In a study done on 114 obese patients with type 2 diabetes submitted to a 12-month follow-up after a 10–16-week behavioural weight-control programme, only 27 patients (24%) who succeeded in obtaining a prolonged weight reduction above 6·9 kg

exhibited a significant reduction in HbA_{1c} levels after 1 year.[46] The authors of a recent consensus statement recognised that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain metabolic goals, either because of failure to lose weight, weight regain, progressive disease, or a combination of factors.[47]

In agreement with previous data,[8] the placebo-subtracted weight loss at 1 year of treatment with 20 mg/day rimonabant was 3·9 kg in the present study in patients with diabetes compared with 4·7 kg and 5·4 kg reported in patients without diabetes.[17–19] Due to its unique mode of action and because of the absence of head-to-head trials, comparison of the results obtained with 20 mg/day rimonabant with those reported with orlistat or sibutramine should be cautious. Nevertheless, this study shows greater weight loss and HbA_{1c} reduction than those reported in a recent meta-analysis of sibutramine or orlistat trials in patients with type 2 diabetes and similar demographic characteristics (ie, age, sex, and body-mass index), but higher baseline HbA_{1c} levels (9·1–9·3% instead of 7·3% in RIO-Diabetes).[48]

20 mg/day rimonabant improved health-related quality of life, especially physical functioning, which points to a positive effect of the drug on this health-related concept.[21] Rimonabant was well tolerated in this study, with adverse events that were generally transient and mild, and much the same as the safety profile reported in non-diabetic patients.[17–19] The most frequent adverse event that led to premature withdrawal in the 20 mg/day rimonabant group was the occurrence of self-reported depression. However, objective measures of depression and anxiety from the HAD scales[25] showed only slight and probably not clinically relevant changes in the 20 mg/day rimonabant group compared with the placebo group. Nevertheless, in this trial, as in other RIO-trials,[17–19] patients with severe psychiatric disorders or receiving antidepressants were excluded, so the safety of rimonabant in such individuals remains to be determined.

There are two limitations to our study. First, although consistent with that of previous 1-year studies in overweight or obese patients,[49] including those done in patients with type 2 diabetes,[48] the retention rate of about 66% in all treatment groups might be considered as rather low. One should note that the dropout rate in this study was lower than in previously reported studies with rimonabant in non-diabetic patients.[17–19] The discontinuation due to reasons other than adverse events was about threefold higher in patients who gained weight than in those who lost weight; this difference was noted in all three treatment arms. Nevertheless, dropouts due to adverse events in the 20 mg/day rimonabant group was much the same in patients who lost weight as in those who gained weight. To take into account the dropout rate, two additional sensitivity analyses, including a repeated measures approach and a BOCF approach, were done, and the results supported the conclusions of the LOCF analysis (figure 2). Second, RIO-Diabetes is a 1-year trial and long-term studies will be needed to assess the effect on diabetes-related complications, especially cardiovascular outcomes.

The results of RIO-Diabetes show the therapeutic value of 20 mg/day rimonabant in patients with type 2 diabetes through effective weight loss, reduced abdominal adiposity, a clinically significant reduction in HbA_{1c} levels, and improvements in HDL-cholesterol, triglyceride, and hsCRP concentrations, and systolic blood pressure. The improvements in HbA_{1c} and HDL-cholesterol concentration levels were twice that expected from the weight loss alone, consistent with the direct peripheral metabolic effects of the drug. These findings support the use of 20 mg/day rimonabant, in addition to diet and exercise, as a new approach to improve glucose control and reduce a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes that is inadequately controlled with metformin or sulphonylureas.

Contributors

A J Scheen, N Finer, and L F Van Gaal were involved in the study concept and design. All named authors participated in the study and contributed to the analysis and interpretation of data, and to the drafting, development, and critical revision of the manuscript. The final version of the manuscript was seen and approved by all authors.

Conflict of interest statement

A J Scheen is a consultant for sanofi-aventis, AstraZeneca, GlaxoSmithKline, and Merck-Santé, and has received lecture fees from sanofi-aventis. N Finer is a consultant for Novartis, Shionogi, Merck, Abbott, sanofi-aventis, Ajinomoto, and GlaxoSmithKline, and has received lecture fees from Abbott, sanofi-aventis, Roche, and Novo-Nordisk. He has also received grant support from Merck, Novartis, Roche, the EU Framework 6 'Diabesity' grant, Alizyme, Abbott Laboratories, and sanofi-aventis. P Hollander is a consultant for, and has received lecture fees from, sanofi-aventis and Pfizer. M D Jensen is a consultant for sanofi-aventis, Metabolic Pharmaceuticals, Novartis, MetaCure, Shionogi USA, and Merck, and has also received grant support from the US National Institutes of Health. L F Van Gaal is a member of advisory boards for sanofi-aventis, Abbott Pharma, and E Lilly and Co. He has received lecture fees from sanofi-aventis and Abbott Pharma, and has grant support from Fonds voor Wetenschappelijk Onderzoek (Scientific Research Council, Flanders, Belgium).

RIO-Diabetes Study Group

Data and safety monitoring board—Alain Leizorovicz, Michael Weintraub, Jean-Louis Imbs, Elliot Danforth, David P L Sachs. *RIO-Diabetes investigators—Argentina:* León Efraín Litwak, Isaac Sinay, Mauricio Jadzinsky, Julio Andrés Vallejos, Jorge Noberto Waitman, Jorge Daniel Herrera, Hugo Fideleff; *Belgium:* Luc Van Gaal, Isabelle Dumont, André Scheen, Francis Duyck, Maximilien Kutnowski; *Canada:* Jean-Pierre Després, Ronnie Aronson, Robert Verdonk, Bruno St Pierre, Ehud Ur, Ginette Girard, Guy Tellier, Ronald Goldenber, Ben Lasko, Isabelle Perreault, Dominique Garrel, Jiri Frohlich, Geeta Achyuthan, Stuart Ross, Laurie Breger; *Czech Republic:* Vojtech Hainer, Lubos Sobotka, Zdenek Rusavy, Dalibor Zeman; *Finland:* Sirkka-Maaret Keinänen-Kiukaaniemi, Aila Rissanen, Leo Kalevi Niskanen; *France:* Jean-Louis Schlienger, Daniel Bensoussan, Guillaume Charpentier, Paul Valensi, Charles Couet, Jean-François Luc Gautier, Max Rieu, Christine Lemaire, Patrice Gross, Claude Le Devehat, Nathan Abenhaim, Michel Bismuth, Denis Tamineau, Jean-Marc Kunh; *Germany:* Jens Jordan, Hans-Gerd Dammann, Hendrik Lehnert, Gerhard Klausmann, Peter Weisweiler, Volker Schusdziarra, Annette Chen-Stute, Stephan Maxeiner, Hans-Christoph Treiche; *Netherlands:* Elisabeth Maria Hubertina Vliegen, M L Drent, R J M Van Leendert, A Van De Wiel, P W E Haeck,

M Castro Cabezas, J J C Jonker, H Kopperschaar; Poland: Ida Kinalska, Ewa Semetkowska-Jurkiewicz, Krzysztof Strojek, Jerzy Loba, Joanna Niegowska, Danuta Zytkiewicz-Jaruga; *UK:* Nicholas Finer, Sudesh Kumar, John Broom, Michael E J Lean, John Wilding, John P D Reckless, Peter Kopelman, Caroline Naik, Jean M K Fraser; *USA:* M Angeli Adamczyk, Andrew J Ahmann, Jacques D Barth, Jerry Drucker, Brent M Egan, Elizabeth M Gallup, Susan N Greco, Ali Iranmanesh, Adesh K Jain, Michael D Jensen, Rashid K Khairi, Andrew J Lewin, John Paul Lock, N Martin Lunde, Thomas C Marbury, James M McKenney, Patrick M Moriarty, Michael J Noss, Thomas J R O'Barr, Leann Olansky, R Walter Powell, Michele D Reynolds, Jeffrey B Rosen, Simona Scumpia, Norman G Soler, Richard L Weinstein, James H Zavoral, Scherwyn L Schwartz, Theodore Feldman, Timothy R Smith, Mildred V Farmer, W Thomas Garland, Priscilla Hollander, Helmut O Steinberg, Brian D Geary, Amin Radparvar, Stephen W Halpern, Oscar Verzosa, Eli M Roth, Steven Landgarten, Barry C Lubin, Wayne E Larson, F Timm III McCarty, Samuel M Lederman, Dennis C McCluskey, Robert G Cesarec, K Stan Self, Martin J Conway, Stephen S Brady, Ronald V Eliosoff, Andrea J Ramsay, John Rubino, Diane K Smith, Robert J Weiss, Alan J Kivitz, H Jackson Downey, Richard E Mills, James W Snyder, Albert J Razzetti, David J Morin, Paul C Tung, Richard V Albery, Scott D Bleser, Donald L Anderson, Curtis J Mello, Lisa Harris, Gerald E Miller, Philip A Snell, Thomas W III Littlejohn, Leah Schmidt, M Scott Touger, Lydia G Corn, Steven K Elliott, Donald Schumacher, William Randall Cox, Barry S Horowitz, Mark S Franklin, E Walter Hood, L Michael Bolognese, Bruce E Henson, Robert Lang, Mark W Layton, Ronald Rapoport, Louis L Shane, Jack D Wahlen, Mohammed Saad, Theodore G Duncan.

Acknowledgments

RIO-Diabetes was sponsored by Sanofi Synthelabo Research, a division of Sanofi Synthelabo Inc, a member of the sanofi-aventis group. Editorial support for this article was provided by Sanofi Synthelabo Research.

References

1 Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003; **52:** 1210–14.

2 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106:** 3143–421.

3 Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339:** 229–34.

4 Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 2006; **368:** 29–36.

5 Scheen AJ. Current management strategies for coexisting diabetes mellitus and obesity. *Drugs* 2003; **63:** 1165–84.

6 Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: case-control study. *Lancet* 2005; **366:** 1640–49.

7 Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; **17:** 961–69.

8 Wing RR, Marcus MD, Epstein LH, Salata R. Type II diabetic subjects lose less weight than their overweight nondiabetic spouses. *Diabetes Care* 1987; **10:** 563–66.

9 Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology* 2004; **47** (suppl 1)**:** 345–58.

10 Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 2001; **410:** 822–25.

11 Ravinet Trillou C, Arnone M, Menet C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol* 2003; **284:** R345–53.

12 Poirier B, Bidouard JP, Cadrouvele C, et al. The anti-obesity effect of rimonabant is associated with an improved serum lipid profile. *Diabetes Obes Metab* 2005; **7:** 65–72.

13 Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* 2003; **63:** 908–14.

14 Osei-Hyiaman D, DePetrillo M, Pacher P, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest* 2005; **115:** 1298–305.

15 Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. *Int J Obes Relat Metab Disord* 2005; **29:** 183–87.

16 Matias I, Gonthier MP, Orlando P, et al. Regulation, function, and dysregulation of endocannabinoids in models of adipose and β-pancreatic cells and in obesity and hyperglycemia. *J Clin Endocrinol Metab* 2006; **91:** 3171–80.

17 Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; **365:** 1389–97.

18 Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: a randomized controlled trial. *JAMA* 2006; **295:** 761–75.

19 Després JP, Golay A, Sjöström L; Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; **353:** 2121–34.

20 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28:** 412–19.

21 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care* 1992; **30:** 473–83.

22 Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res* 2001; **9:** 102–11.

23 Kolotkin RL, Crosby RD. Psychometric evaluation of the Impact Of Weight On Quality Of Life-Lite Questionnaire (IWQOL-Lite) in a community sample. *Quality of Life Research* 2002; **11:** 157–71.

24 Hill AJ, Rogers PJ, Blundell JE. Techniques for the experimental measurement of human being behaviour and food intake: a practical guide. *Int J Obes Relat Metab Disord* 1995; **19:** 361–75.

25 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–70.

26 Hochberg Y. A sharper Bonferonni procedure for multiple tests of significance. *Biometrika* 1988; **75:** 800–02.

27 Gadbury GL, Coffey CS, Allison DB. Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. *Obes Rev* 2003; **4:** 175–84.

28 Wood AM, White IR, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of a physical activity trial with missing outcomes. *Int J Epidemiol* 2005; **34:** 89–99.

29 Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. *Biometrics* 1998; **54:** 1014–29.

30 International Diabetes Federation. Global guideline for type 2 diabetes. http://www.idf.org/home/index.cfm?node=1457 (accessed Oct 9, 2006).

31 American Diabetes Association. Clinical practice recommendations 2005. *Diabetes Care* 2005; **28** (suppl 1)**:** S1–79.

32 Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation* 2004; **110:** 2952–67.

33 Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321:** 405–12.

34 DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 1092–100.

35 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348:** 383–93.

36 Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; **365:** 1333–46.

37 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365:** 1415–28.

38 Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350:** 1387–97.

39 Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003; **112:** 423–31.

40 Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? *Diabetes Care* 2003; **26:** 2442–50.

41 Sattar N, Wannamethee G, Sarwar N, et al. Adiponectin and coronary heart disease: a prospective study and meta-analysis. *Circulation* 2006; **114:** 623–29.

42 Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 2000; **23:** 1499–504.

43 Guare JC, Wing RR, Grant A. Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. *Obes Res* 1995; **3:** 329–35.

44 Anon. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352:** 837–53.

45 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.

46 Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med* 1987; **147:** 1749–53.

47 Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; **29:** 1963–72.

48 Norris SL, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2004; **164:** 395–404.

49 Padwal R, Li S, Lau D. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obes Relat Metab Disord* 2003; **27:** 1437–46.